Chapter 10

TOXIC INHALATIONAL INJURY AND TOXIC INDUSTRIAL CHEMICALS

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INTRODUCTION

Toxic industrial chemicals (TICs) are a wide variety of lung-damaging chemical agents used in manufacturing. TICs are commonly found in communities of industrialized nations that manufacture petroleum, textiles, plastics, fertilizers, paper, pesticides, and many other products. These extensively used chemicals are inexpensive; easily acquired; and transported by ship, train, pipeline, and truck, making them an obvious choice for terrorists. The list of these chemicals is extremely long. According to the North Atlantic Treaty Organization, TICs are chemicals at least as poisonous as ammonia that are produced in large quantities. By this definition, TICs could be released in sufficient quantities to produce mass casualties on or off the battlefield.

The toxicity of TICs varies greatly: some are acutely toxic, whereas others have little toxicity. They come in liquid, vapor, and solid form (Table 10-1); the liquid and vapor forms generally lead to the greatest intensity of exposure. A crucial aspect of the medical management of acute toxic inhalational casualties is determining the respiratory system compartment or compartments affected, then treating the compartmental damage, rather than adhering to a specific treatment protocol for each agent. Knowing the identity of the specific TIC released is helpful but not necessary in the medical evaluation of the pulmonary agent casualty, which should concentrate on the location of lung compartment damage.

Clinical recognition of damage to the central compartment or the peripheral compartment or both should be enough to guide medical management in the absence of identification of specific chemicals.

Determining the damaged compartment is done on the basis of the chemical's aqueous solubility, chemical reactivity, and dose received. Lung-damaging TICs can cause damage to central or peripheral compartments of the respiratory system. The central compartment of the respiratory system consists of the conducting airways, larynx, trachea, and bronchi. The peripheral compartment consists of the smaller airway, in which gas exchange takes place. Effects of agents that act on the peripheral airway are found in the bronchioles to the alveoli of the respiratory system. Centrally acting TICs normally form strong acids or bases (alkali) with the water in the central airway tissues, which leads to the destruction of these tissues. The damaged tissue swells and may slough into the airway, restricting breathing. Ammonia and sulfur mustard are examples of centrally acting TICs. Peripherally acting chemicals cause life-threatening pulmonary edema. However, both centrally and peripherally acting TICs cause damage in the lungs by inhalation. TICs do not affect the lungs when they are absorbed through the skin, injected, or orally ingested. This chapter will be restricted to those chemical agents with acute local pulmonary effects.

TABLE 10-1

DEFINITIONS OF AIRBORNE TOXIC MATERIAL

Gas	The molecular form of a substance, in which molecules are dispersed widely enough to have little physical effect (attraction) on each other; therefore, there is no definite shape or volume to gas.
Vapor	A term used somewhat interchangeably with gas, vapor specifically refers to the gaseous state of a substance that at normal temperature and pressure would be liquid or solid (mustard vapor or water vapor compared with oxygen gas). Vaporized substances often reliquefy and hence may have a combined inhalational and topical effect.
Mist	The particulate form of a liquid (droplets) suspended in air, often as a result of an explosion or mechanical generation of particles (by a spinning disk generator or sprayer). Particle size is a primary factor in determining the airborne persistence of a mist and the level of its deposition in the respiratory tract.
Fumes, Smokes, and Dusts	Solid particles of various sizes that are suspended in air. The particles may be formed by explosion or mechanical generation or as a by-product of chemical reaction or combustion. Fumes, smokes, and dusts may themselves be toxic or may carry, adsorbed to their surfaces, any of a variety of toxic gaseous substances. As these particles and surfaces collide, adsorbed gases may be liberated and produce local or even systemic toxic injury.
Aerosol	Particles, either liquid or solid, suspended in air. Mists, fumes, smokes, and dusts are all aerosols.

The potential for accidental or deliberate exposure to lung-damaging TICs exists for the military and civilian populations. These industrial chemicals provide effective and readily accessible materials to develop improvised explosives, incendiaries, and poisons.[1] On April 30, 2007, newspapers around the world reported an incident in Ramadi, Iraq, in which insurgents exploded a tanker loaded with chlorine gas, causing many civilian deaths and injuries. This chapter will help to prepare the military medical community to recognize the symptoms of lung-damaging TICs and provide treatment.

HISTORY AND USE

Military Uses

The use of chemical or even biological warfare agents goes back to antiquity. Early agents of choice were smokes, which could be generated from a combustible source and serve as a formidable offensive weapon in favorable wind conditions. The Greeks were known to expose their enemies to concoctions of smoke and flame mixed with sulfur.[2] In 1456 arsenical smokes were used defensively in Belgrade against the Turks.[3] During World War I chemical agents such as phosgene, chlorine, sulfur mustard, diphosgene (trichloromethyl-chlorformate), diphenylarsine, chloropicrin, and diphenylchloroarsine were used offensively by both the Allies and the Axis to produce mass casualties.

These agents were largely used in some combination for ease of use and to maintain the persistence of the gas on the battlefield to attain the greatest exposure effects. For example, phosgene, the principal nonpersistent gas, had to be cooled in salt brine during the mixing process because of its low boiling point (8°C), so it was combined with either chlorine or diphosgene for more efficient weaponization.[4] Phosgene was the gas of choice because of its well-known toxicity and capacity to produce the most casualties. Battlefield exposure to gas mixtures such as chlorine-phosgene was responsible for approximately 71,000 casualties or about 33% of all casualties entering the hospital; however, phosgene was reportedly directly responsible for only 6,834 casualties and 66 deaths[4] (this contradicts some reports that suggest phosgene alone was responsible for nearly 80% of all gas casualty deaths during 1914–1918[5]). Although the number of fatalities was low, phosgene gassing during the war caused men to lose 311,000 days to hospitalization, equal to 852 person-years.[4] Because chemical warfare agents are used not solely to exterminate the opposition, but also to take soldiers off the battlefield, phosgene was an effective agent. France first weaponized phosgene in 1916, and Germany quickly followed, choosing to combine phosgene with diphosgene because its higher boiling point (128°C) made the concoction easier to pour into shells. Also, diphosgene was believed to break down to phosgene under proper conditions, especially when it reached the lung.[6]

During the latter course of the war, thousands of chemical agent shells were fired by both sides. The largest number of American casualties from one artillery attack occurred at the Battle of the Marne on June 14–15, 1918, when 1,559 soldiers were gassed.[6] Later that year, on August 2, the Germans fired 20,000 shells, which produced 349 casualties, and on August 7 and 8, they used 8,000 to 10,000 gas-filled shells, producing over 800 casualties and 47 deaths.[6] Table 10-2 gives an overview of the chronological use of chemical warfare agents in World War I.

Because of the massive battlefield casualties and the long-term postwar health effects from the chemical weapons in World War I, the Geneva Protocol was established to ban the use of offensive chemicals in war. The ban was neither generally accepted nor adhered to by all countries, and it was not ratified by the United States until 1975. Egypt reportedly used chemical agents in Yemen between 1963 and 1967, and evidence cites the use of CS (tear gas [2-chlorobenzylidene malonitrile]) and Agent Orange (a plant defoliant) by US forces in Vietnam in the late 1960s and early 1970s.[7]

Nonmilitary Uses

The chemical agents discussed above, used as incapacitating agents or weapons of mass casualty, also have important uses as industrial chemical intermediates or are the end products of nonweapons manufacturing processes. The large number of potentially toxic gases described below and listed in Table 10-3 are limited to those that have been studied under experimental conditions and have an associated human exposure/treatment database.[8]

Ammonia, a naturally occurring soluble alkaline gas, is a colorless irritant with a sharp odor. It is widely used in industrial processes, including oil refining as well as the production of explosives, refrigerants, fertilizers, and plastics. Ammonia is also used as a fixative in photographic, blueprinting, and duplicating processes. It is a particularly significant airborne environmental hazard in swine and poultry confinement areas. Another source of exposure can be from well-known ammonium-based cleaning agents. Ammonia is transported daily by rail and road across the

TABLE 10-2

CHEMICAL AGENTS USED IN WORLD WAR I (IN CHRONOLOGICAL ORDER)

Agent	Type	First Use	Agent	Type	First Use
Ethyl bromoacetate	I	Aug 1914	Trichloromethyl chloroformate	R	May 1916
o-Dianisidine chlorosulfonate	I	Oct 1914	Hydrogen cyanide	R	Jul 1916
Chloroacetone	I	Nov 1914	Hydrogen sulfide	R	Jul 1916
Xylyl bromide	I	Jan 1915	Chloropicrin	R	Aug 1916
Xylylene bromide	I	Jan 1915	Cyanogen bromide	R	Sept 1916
Benzyl bromide	I	Mar 1915	Cyanogen chloride	R	Oct 1916
Chlorine	R	Apr 1915	Phenylcarbylamine chloride	—	May 1917
Bromine	R	May 1915	Diphenylchlorarsine	I	Jul 1917
Methyl chlorosulfonate	I	Jun 1915	Bis(2-chloroethyl) sulfide	S	Jul 1917
Ethyl chlorosulfonate	I	Jun 1915	Phenyldichloroarsine	I	Sept 1917
Chloromethyl chloroformate	I	Jun 1915	Bis(chloromethyl) ether	R	Jan 1918
Dichloromethyl chloroformate	I	Jun 1915	Bis(bromomethyl) ether	R	Jan 1918
Bromoacetone	I	Jun 1915	Thiophosgene	I	Mar 1918
Bromomethylethylketone	I	Jul 1915	Ethyldichloroarsine	S	Mar 1918
Iodoacetone	I	Aug 1915	Methyldichloroarsine	S	Mar 1918
Dimethyl sulfate	I	Aug 1915	Diphenylcyanoarsine	I	May 1918
Perchloromethyl mercaptan	R	Sep 1915	*N*-ethylcarbazole	I	Jul 1918
Ethyl iodoacetate	I	Sep 1915	α-Bromobenzylcyanide	I	Jul 1918
Benzyl iodide	I	Nov 1915	10-Chloro-5,10-dihydro-phenarsazine	I	Sep 1918
Phosgene	R	Dec 1915	Phenyldibromoarsine	I	Sep 1918
o-Nitrobenzyl chloride	I	1915	Ethyldibromoarsine	S	Sep 1918
Benzyl chloride	I	1915	Cyanoformate esters	—	1918
Acrolein	I	Jan 1916			

I: primary irritant; R: lethal via respiratory route; S: mainly skin effects; —: no data.
Data source: Beswick FW. Chemical agents used in riot control and warfare. *Hum Toxicol*. 1983;2:247-256.

country. Industrial exposure of approximately 1,700 parts per million (ppm) of ammonia has been shown to cause severe airway obstruction.[9]

Chlorine, a greenish to yellowish compound, is another irritant gas. Chlorine was used as a chemical warfare agent during World War I because of its heavier-than-air capacity to occupy low-lying areas such as trenches. Chlorine is widely used in the paper and pulp mill production industries; over 10 million tons of chlorine are manufactured in the United States and Europe each year.[10] Accidental exposure to chlorine can occur in the household or anywhere bleach is mixed with acidic cleansers in an unventilated room. Other common sources of exposure are swimming pools, where an imbalance in mixing or dilution can result in increased release of chlorine gas. Since World War I over 200 major incidents involving mild to toxic chlorine exposure have occurred worldwide.[11]

Intentional exposures are not limited to the battlefield. Irritating, poorly water-soluble smokes such as CS, CN (chloroacetophenone), and CR (dibenz[b,f]-1,4-oxazepine), commonly referred to as riot control agents or tear gas, have been used for many years to quell social disturbances. CS was first introduced in Britain by Corson and Stoughton in 1958 to replace CN for riot control because it was safer and more effective.[12] These gases effect the sensory nerves of the skin and mucosa in the nose, eyes, and mouth, causing uncomfortable irritation at the sites of exposures. The overall effects of CS and CN inhalation are respiratory and ventilatory depression. CS has also been linked to reactive airways dysfunction syndrome (RADS) resulting from a single intentional exposure.[13] These agents have no practical use in the chemical and manufacturing industries. Olajos and Salem have provided a review of the tear gases.[14]

Hydrogen cyanide (HCN) is one of the gases most toxic to humans. It may be encountered in industrial processes as sodium or potassium cyanate or as acrylonitrile. Exposures to the salts may occur during the extraction of gold, in electroplating, or in photographic processes. HCN can be manufactured as a byproduct during the synthesis of acrylonitrile, which is a more common industrial hazard used in the production of synthetic rubber and as a fumigant. Mixtures of sodium cyanide, magnesium carbonate, and magnesium

TABLE 10-3

US ARMY CENTER FOR HEALTH PROMOTION AND PREVENTIVE MEDICINE TOXIC INDUSTRIAL CHEMICALS

Chemical	Rate of Onset	Persists in Environment	Toxicity Threshold ppm/hr impairment fatality	Odor	Related hazards / Source Use	Symptoms (from inhalation & dermal Contact)	Decontamination & Treatment
Allyl alcohol (colorless liquid)	Immediate	Days-weeks +	7.7 / 22	mustard-like	Rapidly absorbed through skin highly flammable with caustic fumes; used as contact pesticide. plastic/perfume manufacture	**General Mild Health Effects** Nausea, dizziness, headaches chills, coughing, choking throat irritation	Decontamination: Flush (15min) eyes & skin with water; Soap optional after initial water rinse
Acrolein (colorless-yellow liq)	Immediate	Minutes-hour	0.1 / 1.4	1ppm-sharp acrid, sweet	Toxic and corrosive fumes: Herbicide	**Specific and More Severe Effects** Eyes: Irritation; tearing/watering pain; intolerance to light (eg from hydrogen sulfide)	Treatment & Diagnostic procedures/options: Eye injuries Saline wash Antibiotic ointments
Acrylonitrile (clear/pale yellow liq)	Immediate	Minutes to Hours	35 / 75	17ppm- unpleasant sweet(peach)	Flammable gas; used in plastics, coatings, adhesives idhesives industries; dyes, pharmaceuticals	Skin: (particularly if liquid contact): Irritation; burning; blisters (eg with hydrogen fluoride;	Skin burns/blisters/irritation topical corticosteroids and/or antihistamines inject MgSO₄ at affected
Ammonia (colorless gas)	Immediate	Minutes	110 / 1100	17ppm-sharp suffocating dry urine	Explosives manufacture; pesticides; detergents industry	vesiculation (nitric and sufuric acid) dermatitis; and frostbite (e.g. Acryonitrite)	site (hydrogen fluoride)
Arsine (colorless gas)	Immediate to 24 hours	Minutes to Hours	0.2 / 0.5	0.5ppm garlic like	reacts with H₂0 (don't use H₂0 in fires); Used in electronics industry	**Respiratory Tract/Lungs:** Breathing difficulty, respiratory distress; laryngeal spasm (e.g.	Breathing/respiratory distress: Oxygen and ventilation Prophylactic antibiotics X-rays
Chlorine (greenish-yellow gas)	Immediate to hours	Minutes to Hours	3 / 22	3.5ppm- pungent(bleach) suffocating	Irritating corr fumes; heavier than air; Cleaner/disinfectant in many industries; water treatment; WWI war gas	from hydrogen chloride, or hydrogen bromide); pulmonary edema.	Pulse Ox/ blood gas NOTE: avoid mouth to mouth to protect against cross
Diborane (colorless gas)	Immediate	Minutes to Hours	>1 / 15	2.5ppm-sickly sweet	Very Flammable; Intermediate chemical manufacturing	**Chest/Heart:** chest pain; tachardia (rapid heart beat)	contamination
Ethylene oxide (colorless gas/liq)	Immediate	Minutes to Hours	45 / 200	425ppm-sweet ether-like	Very Flammable Rocket propellant; fumigant sterilization in health care industry	**Systemic; Blood:** Cyanotic (blue skin from lack of Oxygen to blood) (e.g. from	Bronchospasm/Pulmonary Edema: Inhale corticosterioids Beta2 agonist Endotracheal Intubation
Formaldehyde (clear-white gas/liq)	Immediate	Hours	10 / 25	1ppm-pungent suffocating	Flammable; Disinfection/germicide; fungicide; textile; health care (tissue fixing)	SO₂, SO₃, NO₂, ethylene oxide Convulsions/seizures hemolytic anemia;kidney damage (Arsine)	Hemolysis (e.g. Arsine): IV transfusion
Hydrogen bromide (pale yellow liq)	Immediate	Minutes to Hours	3 / 30	2ppm-sharp stinging	Chemical Manufacturing industry; very corrosive	**Additional Chemical Specific Symptoms:**	Seizures: Diazepam
Hydrogen chloride (hydrochloric acid) (pale yellow-colorless liq)	Immediate	Minutes to Hours	22 / 104	0.77ppm pungent ittitation	Corrosive Liquid; Ore, other metal refining/cleaning; food/pickling; petroleum	pink froth/sputum: Ammonia mucoid frothy sputum: SO₂, SO₃, NO₂ Peculiar taste: Ethylene oxide	
Hydrogen Cyanide (colorless-white-pale) (blue gas; liq <°75 F)	Immediate	Minutes	7 / 15-50	1-5ppm-bitter/ sweet almond-like	Weak acide except in Water or mucous membranes-then corrosive/ irritating; used as War gas, pesticide herbicide; other industries	asphyxia and metal taste: Acrylonitrite garlic breath: Hydrogen Selenide	
Hydrogen fluoride (colorless gas/fuming liq)	Immediate & Delayed	Minutes to Hours	24 / 44	0.4ppm-strong irritating	Corrosive liquid, Aluminum & other metal industries, insecticide manufacturing		
Hydrogen selenide (colorless gas)	Immediate	Minutes-hour	0.2 / 1.5+	0.3ppm- decayed horseradish	Highly flammable/explosive; can cause burns/frostbite; decomposes rapidly to form elemental selenium metals & semiconductor prep	⟶	

(**Table 10-3** *continues*)

sulfate are used as rodenticides. Exposure to cyanide can result from the release of HCN gas when the solid mixture comes into contact with water. Exposure to HCN gas, which is lighter than air, can also result from fires because many organic compounds release HCN during combustion or pyrolysis processes.[15] Cyanide, a metabolic poison that smells like almonds, is a po-

tent inhibitor of cytochrome-*c*-oxidase, the terminal enzyme in the mitochondrial electron transport chain required for cellular respiration.[16] Chapter 11, Cyanide Posoning, contains more details on HCN.

Hydrogen sulfide (H_2S), or sour gas, has a well-known pungent and irritating odor that smells like rotten eggs. A heavier-than-air and colorless gas, H_2S

Table 10-3 *continued*

Chemical	Rate of Onset	Persists in Environment	Toxicity Thresholds ppm/hr (impairment / fatality)	Odor	Related hazards/Source Use	Symptoms (from inhalation & dermal contact)	Decontamination & Treatment
Hydrogen Sulfide (colorless gas)	Immediate & Delayed	Minutes to Hours	30 / 100	0.1 ppm- rotten egg	Disinfectant lubrcat/oils; Interm for HC manfacture; deadens sense of smell	**General Mild Health Effects** Nausia, dizziness, headaches, chills, coughing, choking, throat irritation	**Decontamination** Flush (15 min) eyes & skin with water; Soap oprional after initial water use
Methyle Hydrazine	Immediate & Delayed (lungs)	Hours-Days	1 / 3	1-1-ppm- ammonia like	Irritating vapors; Flammable- Once ignited continues to burn; Used as solvent; rocket fuel	**Specific and More Severe Effects** Eyes: Irritation; tearing/watering; pain;intolerance to light (eg from hydrogen sulfide)	**Treatment & Diagnostic procedures/options:** Eye injuries: Saline wash Antibiotic ointments
Hydrazine colorless, oil (fuming) liq/waxy solid or crystals	Immediate & Delayed (lungs)	Hours-Days	13 / 35	3-4 ppm- ammonia like	Flammable- Once ignited continues to burn; irritating vapors; used as solvent; rocket fuel	Skin: (particularly if liquid contact): Irritation; burning; blisters (eg with hydrogen fluoride; vesiculation (nitric & sulfuric acid) dermatitis & frostbite (e.g. Acryonitrile)	Skin burns/blisters/irritation: topical corticosteroids and/or antihistamines inject $MgSO_4$ at affected site (hydrogen fluoride)
Methyle isocyanate (colorless liquid)	Immediate	Minutes-Hours	0.5 / 5	2.1ppm- sharp pungent	intermediate in manufacturing reacts with H_2O (don't use in fire)	Respiratory Tract/Lungs: Breathing difficulty, respiratory distress; laryngeal spasm (e.g. from hydrogen chloride, or hydrogen bromide); pulmonary edma	Breathing/respiratory distress: Oxygen & ventilation Prophylactic antibiotics X-rays Pulse Ox/ blood gas
Methyle mercaptan (colorless gas;liquid <43°F)	Immediate	Minutes-Hours	5 / 23	0,002ppm-rotten cabbage (1ppm odor fatigue)	From decayed organic matter- pulp mills, oil refineries; highly flammable liquid burns/frostbite		
Nitrogen dioxide (colorless gas/pale liq)	Delayed (24-72 hours)	Minutes-Hours	12 / 20	1ppm- ?	Intermediate for manufacture of nitric acid & sulfuric acid; explosives/rocket propellant	Chest/Heart: chest pain; tachardia (rapid heartbeat)	NOTE: avoid mouth to mouth to protect against cross contamination
Nitric acid (colorless, yellow, or red fuming liquid)	Immediate	Hours-Days +	4 / 22+	~1ppm- choking, sweet-acrid	Used in many industries; Very corrosive to skin/mucous membranes as well as metals & other materials	Systemic Blood: Cyanotic (blue skin from lack of Oxygen to blood) (e.g. from SO_2, SO_3, NO_2, ethylene oxide) Convulsions/seizures; hemolytic anemia; kidney damage (Arsine sulfuric acid, hydrazine)	Bronchospasm/Pulmonary Edema: inhale corticosteroids Beta2 agonist Endotracheal intubation
Parathion (pale yellow to brown liq)	Immediate but often Delayed (weeks)	Days-Weeks	0.2 / 0.8	0.04ppm	Organophosphate (insecticide); similar symptoms (and thus treatment) as nerve gases;penetrates leather/canvas & plastic/rubber coatings		Hemolysis (e.g Arsie): IV transfusion
Phosgene (colorless-light yellow gas)	Immediate & Delayed (lungs)	Minutes-Hours	0.3 / 0.8 -5	0.5ppm-musty hay	Dye, pesticide & other industries; Histpry as a war gas; corrosive/irritating	**Additional Chemical Specific Symptoms:** pink froth/sputum: Ammonia mucoid frothy sputum: SO_2, SO_3, NO_2 Peculiar taste: Ethylene oxide asphyxia & metal taste: Acrylonitrile garlic breath: Hydrogen Selenide Miosis, Sweating,↓AchE: Parathion Coffe ground vomit- Sulfuric acid	Seizures: Diazepam
Phosphine (colorless gas)	Immediate & Delayed (lungs)	Minutes-Hours	0.3 / 1.1 -30	0.9ppm-rotten fish, garlic	Insecticide; used in the manufacture of flame retardants & incendiaries		
Sulfuric Acid (clear colorless-brown oily liquid)	Immediate	Hours, Days	2.5 / 7.5	Oderless (acrid taste)	Toxic fumes when heated Battery/dyes/paper/glue/metals industries; volcanic gas		
Sulfur dioxide/trioxide (from sulfuric acide colorless gas)	Immediate & Delayed	Minutes-Hours	>3 / 15-100	1ppm-pungent (metalic taste)	Disinfectant & preserving in breweries & food/canning textile industry; batteries		
Toluene diisocyanate (2.4) (water-white to pale yellow liq, or crystals)	Immediate	Hours-Weeks	0.08 / 0.51	0.4-2ppm-sharp pungent	Skin irritant Polyurethane (wood coatings, foam), nylon industries		

Reproduced from: US Army Center for Health Promotion and Preventive Medicine. *Industrial Chemical Prioritization and Determination of Critical Hazards of Concern.* Aberdeen Proving Ground, Md: USACHPPM; 2003: Appendix B. USACHPPM Report 47-EM-6154-03.

may occur in industrial processes associated with mining, crude oil refining, tanning, farming, paper pulp mills, sewage treatment, and rubber production. It is also a component of natural gas, a major component of volcanic eruptions, and a major airborne hazard in animal confinement areas. H_2S is nearly as toxic as HCN and acts almost as rapidly. It is responsible for more deaths than any other gas.[17] Case reports indicate that exposure can cause neurological symptoms, with focal necrosis of the brain implicated in a fatal outcome.[18] Environmental release of H_2S can cause breathlessness and eye and nasopharyngeal irritation.[19] Reiffenstein et al[20] have provided an early review of H_2S reporting that the typical "rotten-egg" odor is inadequate warning of short-term exposures to high levels, which can cause an inability to smell the gas (olfactory paralysis), among other adverse health effects.

Oxides of nitrogen come in four stable forms: (1) nitrogen oxide (N_2O), an anesthetic compound, and (2) nitric oxide (NO), an important byproduct of intracellular biochemical nitrogen metabolism, which also forms (3) nitrogen dioxide (NO_2) and (4) nitrogen tetroxide (N_2O_4) when oxidized in air. Oxides of nitrogen are important reactive end products of air pollution. The reactive dioxide form is a pulmonary irritant that can be found in fresh silage from agricultural processes preserving green crops such as alfalfa and corn (silo-filler's disease), in unventilated areas with

high temperature arc welding, and the production and transport of nitric acid. N_2O may also be produced in the dipping of aluminum, brass, and copper and in combustion and pyrolysis processes.[21]

Polytetrafluoroethylene (Teflon [Dupont, Wilmington, Del]) can form toxic gases when heated to temperatures above 400°C. Combustion and pyrolysis byproducts of Teflon, which have been known for some time, have been implicated in pulmonary injury and even deaths following a single exposure.[22] Illnesses caused by the inhalation of combustion byproducts have been given the label "polymer fume fever." One of the more common byproducts is perfluoroisobutylene (PFIB), which is reportedly 10 times more toxic than phosgene.[23]

Phosgene has been used extensively for the past 60 years in the production of pharmaceuticals, aniline dyes, polyfoam rubber, isocyanates, and plastic products in the United States and worldwide. In 1998 the United States used 4.3 million pounds of phosgene in manufacturing processes.[24] Phosgene is used in a "phosgenation" reaction to help supply chlorine groups to reaction products. Babad and Zeiler[25] have reviewed phosgene chemical reactions, finding that phosgene rapidly reacts with water to form carbon dioxide and hydrochloric acid, and it also reacts with macromolecules containing sulfhydryl, amine, and hydroxyl groups in aqueous solutions. Phosgene can be formed by the thermal decomposition of chlorinated hydrocarbons and poses a threat for welders, refrigeration mechanics, and automobile mechanics.[26] Commonly used industrial degreasers contain chlorinated hydrocarbons, such as perchloroethylene, which can form phosgene when heated. Therefore, industrial workers, fire fighters, military personnel, and others are at risk for accidental or occupational exposure to phosgene. In Poland, for example, because of heavy industrialization in proximity to densely populated areas, phosgene, along with chlorine, ammonia, and sulfur dioxide, has been identified as one of the most significant threats to the environment.[27]

Smoke is a general classification of a complex mixture of particulate/gaseous emissions. Smokes are products of the combustion process of burning or smoldering. The major cause of death from fire-related events is smoke inhalation. Smoke can include many of the chemicals mentioned earlier. Particulate matter such as carbon soot particles can make up a significant proportion of toxic smoke, as can carbon monoxide, HCN, phosgene, aldehydes such as formaldehyde, ammonia, and PFIB.

Sulfur dioxide is a major air pollutant and a principal source of photochemical smog and acid rain. A colorless, water-soluble gas 2.26 times heavier than water, sulfur dioxide is used in a number of industrial processes such as the smelting production of copper, iron, lead, and zinc ores. When it comes into contact with moist surfaces, sulfur dioxide is hydrolyzed and oxidized to form sulfuric acid. It is extremely corrosive to the nasopharynx region, eyes, and upper airways. Inhalation exposure may progress to acute respiratory distress syndrome (ARDS) and has been implicated in causing RADS.[28] Prolonged exposure causes inflammation of the airways and impairs the immune system and lung resistance.[29] Table 10-4 provides a very limited overview of some well-known gaseous irritants.

MECHANISMS OF TOXICITY

Numerous studies have been undertaken to determine the mechanisms of toxicity and the basis for lung injury from exposure to toxic gases. These investigations have historically involved animal models. As early as 1919 the progression and intensity of exposure to agents such as phosgene was demonstrated in dogs. In later decades, animal models included mice, rats, guinea pigs, swine, and monkeys to more accurately predict the temporal effects of injury progression and scope in humans. Many of these models involved the use of inhalation techniques, focused essentially on the establishment of a fundamental relationship: lethal concentration (C), in ppm, times the duration (T), in minutes, of exposure (also known as Haber's law).[30] The product of C × T corresponds to a standard response measure describing a biological endpoint of edema formation, death, or any other consistent physiological parameter. Conceptually, this product simply meant that the same biological endpoint would occur whether the animals were exposed to 100 ppm of gas for 10 minutes, 50 ppm for 20 minutes, or 20 ppm for 50 minutes (all resulting in a C × T of 1,000 ppm•min). However, later experiments showed that for a gas such as phosgene and other irritants, Haber's law was applicable only over short exposure times.[31,32] It is now generally agreed that concentration rather than duration of exposure determines the gas's effect.

As implied by this discussion of Haber's law, the use of such a general quantitative assessment for exposure-response effects includes inherent problems. Many fundamental physiological, toxicological, histopathological, and biochemical effects are lost in such an evaluation, especially when death is the endpoint. As shown in Table 10–4, many of these compounds have varying solubility ranges, resulting in a range of effects within the pulmonary tree. For example,

TABLE 10-4

MECHANISMS OF LUNG INJURY OF GASEOUS RESPIRATORY IRRITANTS

Irritant Gas	Mechanism of Injury
Ammonia (NH_2) Source: Agriculture, rain, plastic, explosives	Alkali burns
Hydrogen chloride (HCl) Source: Dyes, fertilizers, textiles, rubber, thermal degradation of polyvinyl chloride	Acid burns
Sulfur dioxide (SO_2) Source: Smelting, combustion of coal/oil, paper manufacturing, food preparation	Acid burns
Chlorine (Cl_2) Source: Paper, textile manufacturing, sewage treatment	Acid burns, free radical formation
Oxides of nitrogen (NO, NO_2, N_2O_4) Source: Agriculture, mining, welding, manufacturing of dyes/lacquers	Acid burns, free radical formation
Phosgene ($COCl_2$) Source: Firefighters, welders, paint strippers, chemical intermediates (isocyanate, pesticides, dyes, pharmaceuticals)	Acid burns

Colors indicate water solubility. Red: high; yellow: intermediate; green: low.
Data source: Schwartz DA. Acute inhalational injury. *Occup Med*. 1987;2:298.

inhalation of compounds that have limited solubility results in lower lung injury, whereas compounds that are miscible in water affect the upper regions of the respiratory tree. Compounds discussed earlier, such as phosgene, chlorine, oxides of nitrogen, and PFIB, are considered lower airway (peripheral compartment) irritants based on their solubility characteristics. Gases such as ammonia, sulfur dioxide, and hydrochloric acid are generally considered upper airway (central compartment) irritants but can affect the lower lung regions if exposure concentration and duration are sufficient. Carbon monoxide, H_2S, and HCN are classified as systemic chemical asphyxiants.

Rational and effective medical countermeasures against the inhalational injury caused by gases, smokes, fumes, and mists depend on mechanistic evidence of exposure responses at the tissue and cellular levels. The investigation required to determine the correct treatment route, therapeutic window, and dosing levels is costly and time consuming. Study of representative compounds from a class of gases can provide general insight into the mechanisms responsible for tissue and cellular injury and the subsequent repair processes. In recent years extensive data on the mechanisms of phosgene, chlorine, H_2S, and oxides of nitrogen gas exposure have been published.[32–34] These studies evaluated the following range of effects over time and at various exposures:

- histopathology of exposed lung tissue;
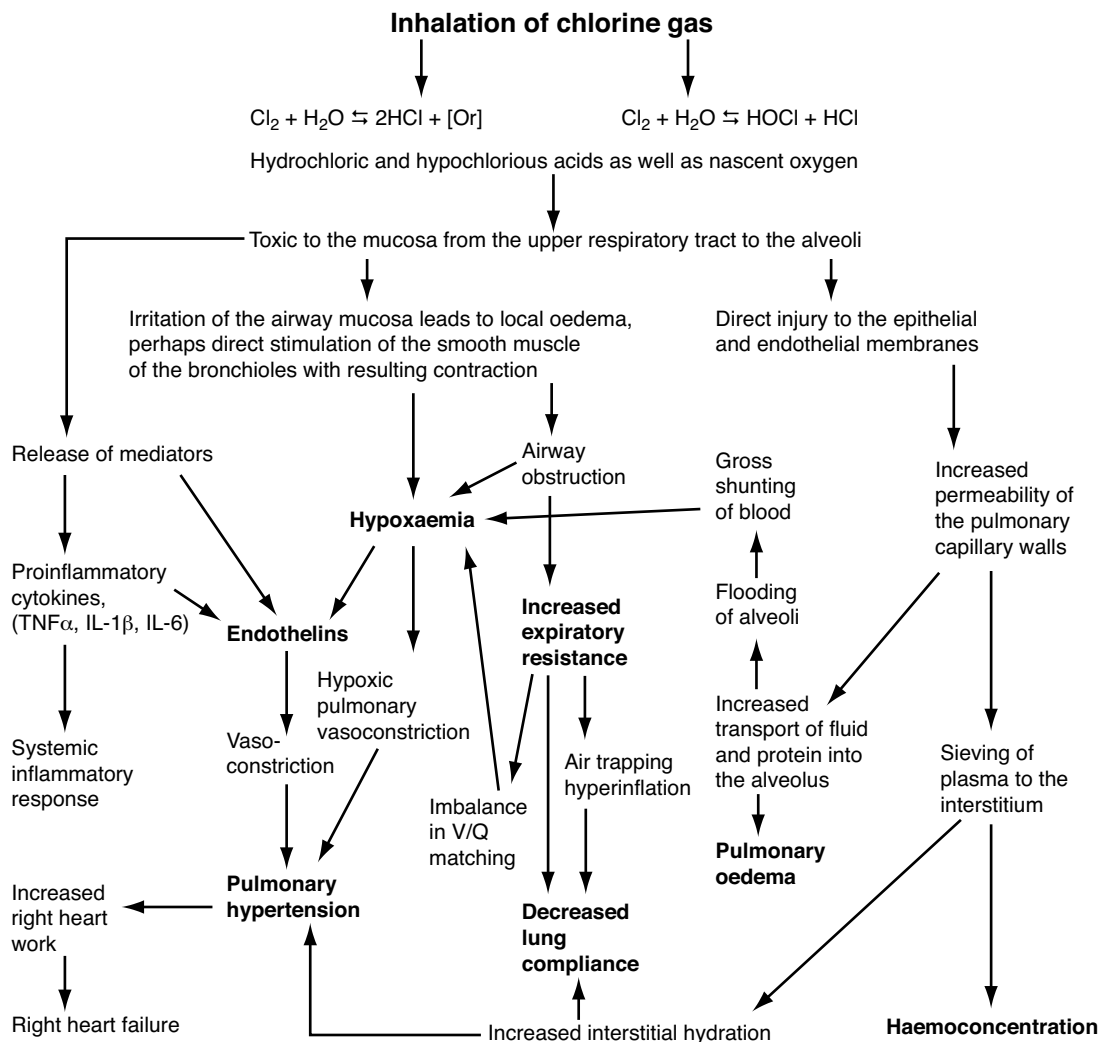- biochemical pathway assessment of lung

tissue markers of exposure such as a simple determination of wet/dry weight ratio for pulmonary edema estimates;
- inflammation pathways;
- metabolic markers of exposure such as arachidonate mediators;
- physiological assessment of blood gas and hemodynamic status;
- cell differential counts;
- pulmonary function as measured by plethysmography;
- tissue and bronchoalveolar lavage fluid redox and antioxidant status;
- behavioral effects;
- genomic expression markers;
- immunosuppression effects; and
- mortality as determined by survival rate studies.

Mechanistic Effects of Inhaled Pulmonary Agents

Exposure to inhaled agents can compromise the entire pulmonary tree through a range of altered physiological, biochemical, and pathophysiological processes. The general mechanisms of toxic gas exposure are shown in Figure 10-1. Researchers have used animal models to examine these dysfunctional pathways in many ways. In an obligate nose-breathing experimental animal like the rodent, the basic mammalian life processes are extrapolated to humans, allowing for reasonable estimates of potential human exposure responses. This chapter will cover studies of prominent pathways through which

Inhalation of chlorine gas

$Cl_2 + H_2O \leftrightarrows 2HCl + [Or]$ $Cl_2 + H_2O \leftrightarrows HOCl + HCl$

Hydrochloric and hypochlorious acids as well as nascent oxygen

Toxic to the mucosa from the upper respiratory tract to the alveoli

Irritation of the airway mucosa leads to local oedema, perhaps direct stimulation of the smooth muscle of the bronchioles with resulting contraction

Direct injury to the epithelial and endothelial membranes

Release of mediators

Airway obstruction

Gross shunting of blood

Increased permeability of the pulmonary capillary walls

Hypoxaemia

Proinflammatory cytokines, (TNFα, IL-1β, IL-6)

Endothelins

Increased expiratory resistance

Flooding of alveoli

Hypoxic pulmonary vasoconstriction

Vaso-constriction

Air trapping hyperinflation

Increased transport of fluid and protein into the alveolus

Increased interstitial hydration

Sieving of plasma to the interstitium

Systemic inflammatory response

Imbalance in V/Q matching

Pulmonary oedema

Pulmonary hypertension

Decreased lung compliance

Increased right heart work

Right heart failure

Increased interstitial hydration

Haemoconcentration

Fig. 10–1. General mechanisms of toxic gas exposure.
IL: interleukin
TNF: tumor necrosis factor
V/Q: ventilation profusion ratio
Reproduced with permission from: Wang J. *Pathophysiology and Treatment of Chlorine Gas-Induced Lung Injury: An Experimental Study in Pigs* [dissertation]. Linköping, Sweden: Linköping University; 2004: 36.

inhaled compounds affect basic life processes.

It should be kept in mind that the effects of an inhalational event are related to the chemical reactivity of the toxicant, its concentration, and the duration of exposure. In accidental exposure scenarios, there is generally poor quantifiable information on concentration and exposure duration; in some cases the identity of the agent may be uncertain. Also, the possibility of multiple simultaneous chemical exposures, which can occur in a chemical plant explosion, must be considered. In Bhopal, India, an accidental release of methylisocyanate used in the production of the pesticide carbaryl was responsible for over 60,000 casualties and nearly 5,000 deaths in December 1984.[35] Inhalation of the toxic gas resulted in a range of pulmonary symptoms that included irritation and coughing. Pulmonary edema and atelectasis were the eventual causes of death. Long-term survivors were diagnosed with lung inflammation, fibrosis, and compromised lung function. Survivors continue to have health issues related to catastrophe event after nearly 25 years.[36]

Physiological Responses

Many studies have shown that the adverse effects

of toxic gas inhalation can easily be assessed by measuring basic pulmonary function. Several irritants such as phosgene, chlorine, and PFIB initiate reactions that result in problems with physiological breathing processes. Cranial nerve input in the nasopharyngeal region is mainly responsible for initiating changes in respiratory function, as evidenced by altered breathing mechanics. Experiments in mice exposed to phosgene show that minute ventilation is increased following exposure,[37] caused by an increase in respiratory rate in response to local irritation from the gas. Inspiratory and expiratory flow rates are also compromised by local sensory irritation because of formation of hydrochloric acid in the mucous membranes in the upper airway of the central airway compartment. Several studies found decreased dynamic compliance and increases in both airway resistance and tracheal pressure to be predictable patterns of response following irritant gas exposure.[38–41] Phosgene exerts much of its toxic effect in the peripheral compartment of the lung, and histopathologic specimens show a significant alteration of the acinar type I and II epithelial cell layers of the air–blood barrier. Exposure causes significant pulmonary edema and respiratory acidosis through increased P_{CO_2} saturation, decreased Pa_{O_2} saturation, and decreased arterial pH.[42–44] Similar responses have been observed in animal models using chlorine, PFIB, and ammonia. Studies involving PFIB have demonstrated that rats made to exercise following exposure exhibited an enhancement of transcellular transport of blood proteins to the alveolar surface.[45,46] These data suggest that although the lung may be injured and edematous, fleeing from the site of exposure may not in itself contribute to the edematous effect.

Decreased body weight is a useful indicator of exposure and systemic toxicity. Pulmonary edema formation can be estimated by the lung wet weight to dry weight ratio, which increases over time as the injury progresses . Although the wet/dry weight ratio is an important measure of edema, it may not show subtle effects that preexist fulminant alveolar edema. A valuable indicator of what is actually occurring in the deep lung environment is bronchoalveolar lavage fluid (BALF). BALF tests provide a wealth of information. Lavage fluid protein levels give a good indication of subtle changes in the integrity of the air–blood barrier. Increased protein levels can be measured in some cases hours prior to gross alveolar edema formation. This may indicate that interstitial edema is occurring. Much use has been made of the electrolyte homeostatic responses to toxic gas exposure. Sciuto et al have shown that phosgene exposure can produce a possibly deleterious effect on lung homeostatic process by altering ionized Ca^{++}, Na^+, and K^+ levels

indirectly, thus indicating possible compromised Na^+, K^+, or Ca^{++}-adenosine triphosphatase pump function.[47] Inhalation of irritants such as phosgene is known to eventually result in immunosuppression, which may increase mortality via infection in the compromised lung.[48,49]

Genomic studies have provided insight into the effects of toxic gas exposure on gene expression levels. In phosgene-exposed mice, it was demonstrated that the earliest changes (occurring within 1 to 4 hours) in lung tissue involved increased expression levels of antioxidant enzymes of the glutathione redox cycle.[50] These data strongly suggest that free-radical–mediated injury processes are active well before gross pathophysiologic changes become manifest. It has been shown that in vitro exposure of epithelial cells to nitrogen dioxide can cause a range of problems in the entire length of the respiratory tract. Many of these detrimental effects are the result of activated reactive nitrogen species free radicals such as the peroxy radical $OONO^-$ or the nitrogen dioxide radical $\bullet NO_2$ itself.[51]

Riot control agents, also called incapacitants, can cause ocular and cutaneous as well as acute pulmonary responses during exposure. Although generally nonlethal, incapacitants may have magnified contact problems if exposure occurs within a confined space. Symptoms resulting from a single exposure can last for years.[8]

Pathophysiological Effects of Exposure

Examination of histopathological effects on chemically exposed lung tissue provides critical information on the effects of a C × T response. The mechanisms of lung injury and repair are summarized in Figure 10-2.[52] Evaluation of phosgene-induced pulmonary injury to the peripheral compartment revealed characteristic temporal acute toxicity lesions. Early lesions of a toxic gas exposure can be characterized by leakage of edema, fibrin, and erythrocytes from the pulmonary microvasculature into the alveolar spaces and interstitial tissues. In general, alveolar and interstitial edema can characterize the earliest and most significant pulmonary changes. Epithelial damage in the terminal bronchioles and alveoli as well as mild inflammatory cell infiltrates can accompany increasing pulmonary edema. The repair and regeneration of epithelial damage centered on the terminal bronchioles may complement the resolution of edema.[53] In this study early indicators of phosgene-induced pulmonary injury were identified by comparing acute pulmonary histopathologic changes to bronchoalveolar lavage and lung wet-weight gravimetric measurements. Of the BALF parameters studied, lactate dehydrogenase and

Mechanism of lung injury and repair.
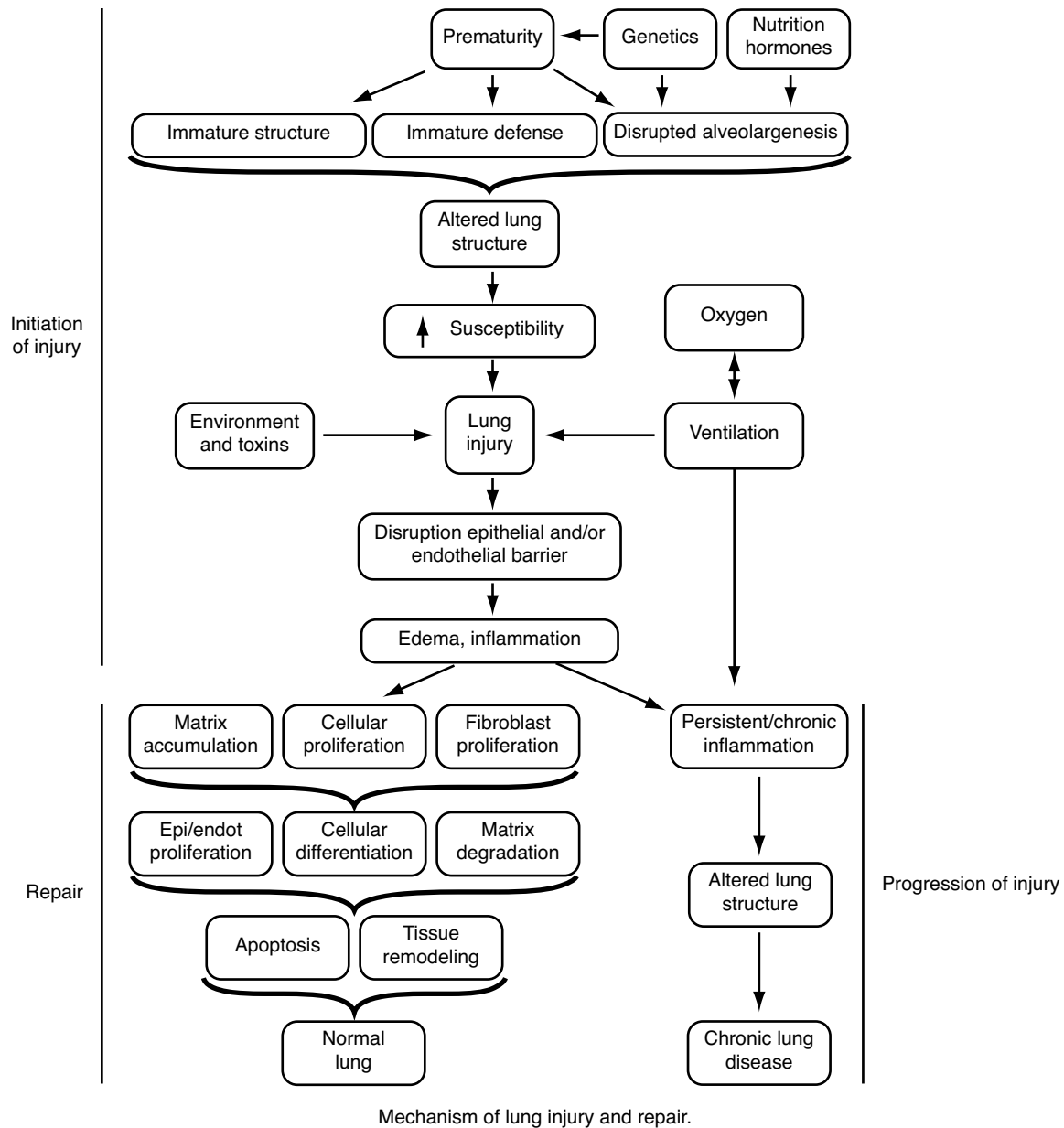
Fig. 10-2. Pathophysiology of toxic gas inhalation.
Epi/Endot: epithelial and/or endothelial
Adapted with permission from: Copland I, Tanswell K, Post M. Principals of lung development, growth, and repair. In: Notter RH, Finkelstein JN, Holm BA, eds. *Lung Injury: Mechanisms, Pathophysiology, and Therapy.* Boca Raton, Fla: Taylor & Francis Group; 2005: 19–66.

protein levels were the most sensitive early indicators of pulmonary edema. In experiments in rats exposed to PFIB, as the mass exposure concentration increased, the earlier tissue injury occurred. Epithelial and endothelial cell blebbing occurred, which progressed over time to endothelial swelling and fenestrations of the epithelial barrier, denudement of the alveolar surface, and interstitial edema.[45] PFIB and phosgene exposure also caused alteration of the production of specific surfactant phospholipids, which can have important implications for reduced lung compliance and the subsequent treatment of this injury.[54] In rats exposed to the pyrolysis products of Teflon at 450°C, ultrastructural changes in the lung consisted of pulmonary edema, hemorrhage, and necrotic tracheobronchial epithelium, accompanied by pneumocyte bleb formation, denuda-

tion, and fragmentation.[55]

Lung tissue and cellular responses to inhalation exposure can also be manifested in the form of cell membrane destruction. This can be measured to some degree by determining the extent of lipid peroxidation, an indicator of oxidative stress caused by the abundance of free radicals. Lipid peroxidation is a process whereby the rigid lipid bilayer of the membrane becomes more fluid, resulting in the activation of intracellular metabolic pathways regulated by altered enzyme function. One of the more important pathways is the arachidonic acid (AA) pathway, which leads to the production of mediators of inflammation and edema such as the leukotrienes. The other metabolic arm of the AA pathway leads to vasoactive compounds such as prostaglandins, which are in part responsible for vascular tone. Both leukotrienes and prostaglandins have been implicated in toxic-gas–induced acute lung injury.[56–59] Adenlyate cyclase is yet another injury-activated enzyme system responsible for the cleavage of adenosine triphosphate to form adenosine 3′,5′-cyclic monophosphate (cAMP), which is required for endothelial and epithelial tight-junction formation. The initial step in this process is damage to membrane surface β-adrenergic receptors, which aid in the regulation of cAMP formation. With the deactivation of cAMP formation, tight junctions become more permeable and allow the passage of fluid or water into intracellular and extracellular spaces. Decreased cAMP production and the resultant pulmonary edema have been implicated in toxic-gas–induced acute lung injury.[39]

Acute exposure to nitrogen dioxide causes a range of pathological effects characterized by increased epithelial permeability and the proliferation of Clara and type II epithelial cells.[60] Chronic exposure induces bronchiolitis, alveolar bronchiolarization, ciliated cysts, and emphysema. Exposure effects may be more pronounced in those with preexisting compromised lung function such as asthma. In experiments in an asthmatic population exposed to 1 ppm nitrogen dioxide, increased levels of mediators of inflammation and vasoactive compounds were measured in the BALF.[61] Metabolites of the cyclooxygenase pathway of the AA cascade, such as 6-keto-prostaglandin F_1-α (responsible for bronchodilation) were decreased; however, both prostaglandin D_2 and thromboxane B_2 (responsible for bronchoconstriction) were increased. Elevated levels of leukotrienes such as C_4, D_4, and E_4, which are products of the lipoxygenase pathway of the AA cascade related to bronchial hyperresponsiveness, were also involved in the inflammatory response.

Exposure to smoke has been shown to cause sufficiently severe acute lung injury to ultimately result in death. In human smoke-related fatalities, the lungs were shown to exhibit soot staining in the tracheobronchial mucosa, and they were heavy (edematous) and hyperemic. Light microscopy indicated pulmonary congestion, and electron microscopy revealed carbon particles as well as interstitial and intraalveolar edema.[62]

Inflammatory Pathways

Inflammation is a critical result of toxic-gas–inhalation injury. Many studies have demonstrated a decrease in the number of macrophages, which are important in clearance mechanisms, and an increase in neutrophils, which aid in detoxification of toxic mediators and metabolites. These shifts in cell populations generally occur over time and are usually a function of the gas involved, the depth of inhalation, the concentration, and the duration of exposure. In the case of some inhaled gases, the chemical reaction in the tissue can produce deleterious amounts of free radicals. These radicals in turn can damage migrating cells such as neutrophils, causing them to dump their toxic proteases, proinflammatory cytokines and chemokines, and additional toxic free radicals such as the hydroxyl species •OH and superoxide anion O_2^- into the intracellular environment, causing greater damage. This additive effect may account for some of the latent injury responses seen following inhalation of gases such as phosgene and possibly other irritants, some of which have well-described latency (1–24 hours) effects.

Markers of inflammation and the timing of their release after exposure can provide useful information about the potential therapeutic window for eventual and successful treatment. Many studies have focused on cytokines, which are produced by a variety of white cells, fibroblasts, and epithelial and endothelial cells, to assess the inflammatory response. Cytokines can have a wide range of proinflammatory and antiinflammatory effects in tissue injury responses. These compounds serve as important mediators of tissue and injury repair processes and as such represent suitable markers of inflammation injury and signal transduction pathways (Table 10-5).[63]

For example, in phosgene-exposed mice, BALF cytokine and chemokine analysis over 72 hours clearly demonstrated that the cytokine interleukin-6 and the chemokine macrophage inflammatory protein-2, the analog in mice for human interleukin-8, were both significantly increased within 4 to 8 hours of exposure.[64] Both interleukin-1β and tumor necrosis factor-α were significantly increased 24 to 72 hours after exposure. The data support the postulation that tumor necrosis

TABLE 10-5

MAIN INFLAMMATORY AGENTS INVOLVED IN ACUTE LUNG INJURY, THEIR SOURCE AND ACTION

Agent	Source	Actions
Cytokines (Proteins)		
IL-1	In response to infection/injury from activated macrophage. Induced by TNF from mononuclear and endothelial cells.	Regulates systemic inflammatory response, causes increase in blood neutrophils; causes fever. Induces other cytokines. Stimulates NO production, produces PLA_2, PAF, releases histamine.
IL-6	Induced by IL-1 from epithelial cells.	Creates pyrogen, activates stromal bone marrow to produce CSF.
IL-8	Secreted by macrophages, endothelial cells, T cells and fibroblasts in response to LPS, IL-1 or TNF stimulation.	Chemotactic for neutrophils and activates macrophages.
TNF-α	Large amounts from endotoxin-stimulated macrophages.	Induces arachidonic metabolites and synthesis of cytokines. Chemotactic for neutrophils and macrophages. Synergistic with IL-1. Causes fever.
Lipids (Arachidonic Acid Metabolites)		
Leukotrienes (B_4, C_4, D_4, E_4)	Enzymatic pathway from membrane phospholipid.	Causes vasoconstriction, bronchoconstriction, enhancement of capillary leakage.
Prostaglandin E_2	Enzymatic pathway from membrane phospholipid.	A vasodilator, has proinflammaotry and antiinflammatory potential.
Thromboxane A_2	Enzymatic pathway from membrane phospholipid.	Potent vasodilator, causes platelet sequestration.
PAF	Epithelial cells via the arachidonic acid pathway, also neutrophils, basophils and platelets.	Causes platelet aggregation. Recruits eosinophils, causes vasodilation, increases vascular permeability, causes degranulation of neutrophils. Spasmogenic on bronchial smooth muscle.
Reduced Oxygen Species (Free Radicals)		
OH, H_2O_2, superoxide anion	LPS stimulated macrophage/monocyte cell.	Very reactive, responsible for lung tissue injury. Interacts with arachidonic acid pathway to increase levels of eicosanoids.

CSF: colony-stimulating factor
H_2O_2: hydrogen peroxide
IL: interleukin
LPS: lipopolysaccharide
NO: nitric oxide
OH: hydroxyl radical
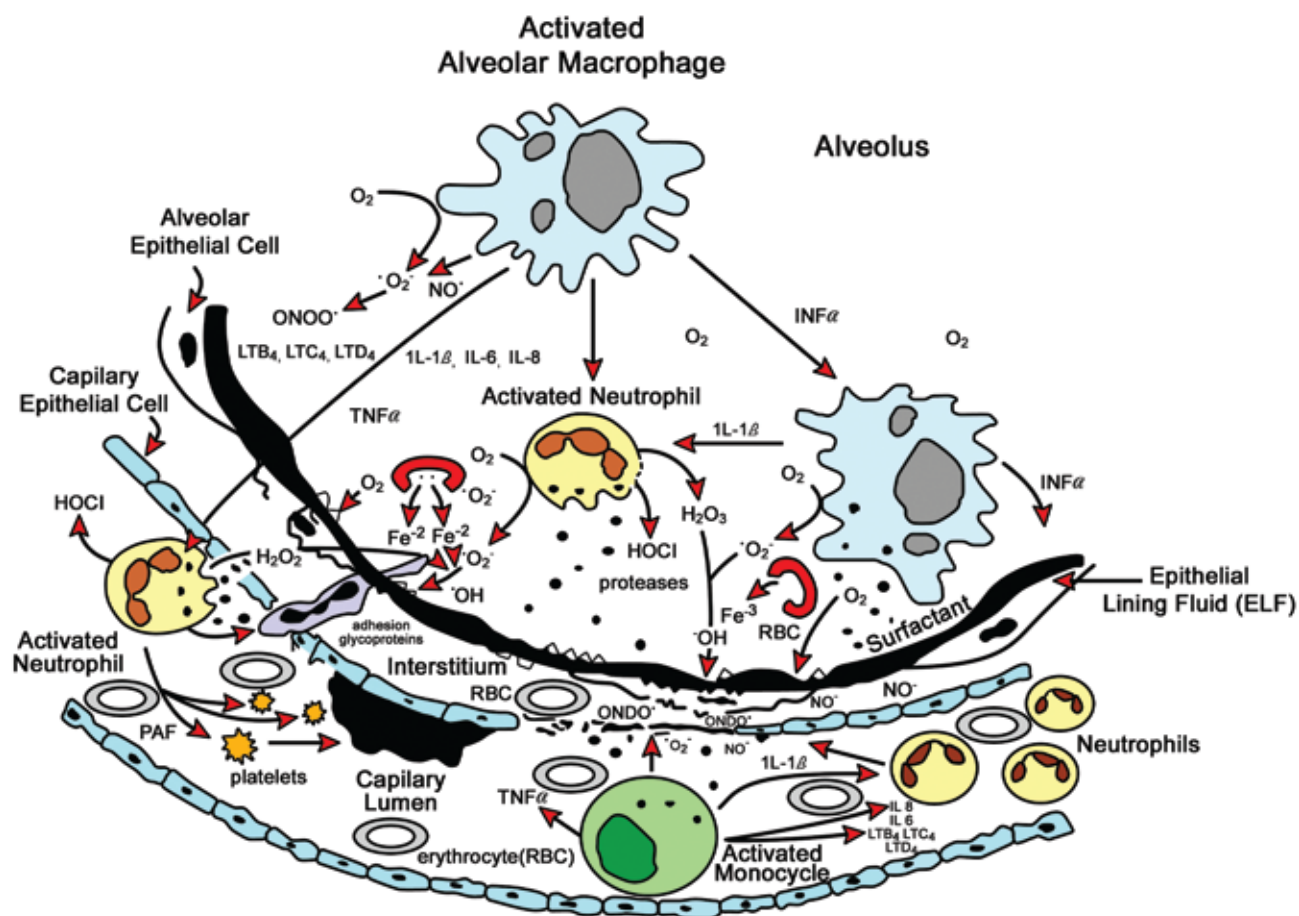PAF: platelet-aggregating factor
PLA_2: phospholypase A2
TNF: tumor necrosis factor

factor-α may aid in fluid clearance in this injury model. The nature of lung injury in response to an inhalational event can be extremely complex. Figure 10-3 provides a visual representation of the alveolar region of the peripheral lung compartment following exposure to toxic gas. The difficulty in treating an injury with a large array of metabolic chaos is that many of these pathways are activated and on-going simultaneously.

Biochemical Responses

Understanding the biochemical responses to inha-

Fig. 10–3. General schema for the study of acute and chronic lung injury.
HOCl: hypochlorous acid
INF: interferon
H_2O_2: hydrogen peroxide
H_2O_3: dihydrogen trioxide
IL: interleukin
LT: leukotriene
PAF: platelet-aggregating factor
RBC: red blood cell
TNF: tumor necrosis factor
Courtesy of: US Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Md.

lation exposure can provide a wealth of information about pathways that may lead to successful treatment strategies. One of the most important pathways is the glutathione (GSH) cycle. GSH is an important and ubiquitous intracellular antioxidant. The GSH redox cycle is activated in response to free-radical–mediated tissue and cellular injury. GSH also aids in maintaining the proper balance between naturally occurring free radical metabolism processes and antioxidant detoxification. Basically, it helps to create equilibrium in the antioxidant/oxidant ratio. Exposure to inhaled

chemical toxins can elicit a response that favors the liberation of extremely toxic free radicals. Exposure to phosgene has been demonstrated to cause a significant decrease in lung tissue GSH across a range of species.[65] Concurrent with decreased GSH protection in the lung tissue, BALF shows a marked increase in GSH levels.[65] Increased BALF GSH is believed to be a response of damaged lung tissue for the purpose of transporting GSH to critical areas in the alveolar regions. This occurs to protect the surfactant and epithelial integrity of the gas-exchanging units in response to free radi-

cal activity. This same response mechanism has been demonstrated in smokers.[66] It is well established that the toxic effect of smoking is largely a free radical-mediated process.

SPECIFIC INHALED TOXIC-GAS–INDUCED EFFECTS AND THEIR TREATMENTS

Defining treatment strategies and clinical medical management for toxic gas exposure is problematic. In most cases the chemical inhalant is unknown. In other cases there may be multiple chemical exposure, patients may be too confused to accurately recall the duration of inhalation, and the patient's health and age may affect the outcome. Many chemicals can cause hyposmia or even anosmia following inhalation, making the assessment of duration and type of chemical agent inhaled all the more difficult. Some individuals are known to be much more chemically sensitized than others, especially if, for example, asthma, smoking, or an acquired sensitivity is present. Many of the chemicals discussed thus far are listed as causing RADS or occupationally-induced asthma.[67,68] Currently, most doctrines describe management, including ventilation support, pulmonary function tests, chest radiographs, supportive fluid replacement, and antiinflammatory treatment. The mechanisms of toxicity in acute lung injury processes are largely consistent from chemical to chemical, and injuries detected early will respond more readily to supportive or specialized treatment. Several compounds for which experimental or even clinical supportive therapy has been successfully used are detailed below.

Ammonia

Inhalation exposure to ammonia, generally considered a central airway compartment irritant, can cause damage to the airway epithelium and the alveolar-capillary membrane. Acute signs and symptoms of inhalation, typical of irritant gases, include coughing, bronchospasm, difficulty in breathing, pulmonary edema, hypoxemia, and respiratory failure.[69] At death, hemorrhagic pulmonary edema can be a hallmark of exposure. Interstitial fibrosis has been observed in patients following accidental exposure to ammonia.[70]

In rabbits exposed to nebulized ammonia at an estimated accidental exposure level (35,000–39,000 ppm over 4 minutes), acute and severe lung injury occurred. Decreased Pa_{O_2} and increases in airway pressure and Pa_{CO_2} were evident from 1 to 6 hours after exposure.[69] In this experimental model, the use of inhaled corticosteroids such as budesonide administered 30 minutes after exposure was not effective in improving gas exchange or reducing elevated airway pressure. Corticosteroids are controversial for therapy following ammonia inhalation and ingestion exposure in humans.

Chlorine

Affecting both the central and peripheral airway compartments, chlorine inhalation leads to abrupt bronchoconstriction, increased airway resistance, and decreased compliance. In humans who have died from chlorine poisoning, severe pulmonary edema, pneumonia, and ulcerative tracheobronchitis have been seen.[71] Recently, epithelial cell necrosis, small airway dilation, and microvascular permeability have been found.[44] Efficacious therapeutic treatments have been tested in experimental models using large swine. Aerosolized terbutaline or the corticosteroid budesonide reduced acute lung injury when administered 30 minutes after a 400 ppm × 20-minute exposure.[72] Lung function was improved even more when both compounds were administered in combination. The effect of terbutaline or budesonide corroborates the biochemical response mentioned earlier: terbutaline helps increase cAMP levels through the stimulation of β-adrenergic signaling pathways and adenylate cyclase, thereby increasing tight junction strength and the integrity of the air–blood barrier, which reduces fluid transport through compromised basement membranes. Budesonide can work by reducing proinflammatory cytokines and by stabilizing membranes by limiting the effects of membrane lipid peroxidative processes and the subsequent release of reactive mediators.

Hydrogen Cyanide

As a metabolic poison, HCN presents a challenge for effective postexposure treatment. It is also considered to be a cardiotoxin. Acute exposure to HCN rarely causes specific changes in histopathological or pathological changes.[73] Many people believe that the slightest contact with HCN means instant death, but studies of experimental animals have disproven this belief. Sublethal concentrations can produce incapacitation, with dizziness and nausea reported in some exposed people.[74] However, treatment should always be provided as rapidly as possible. Supportive and antidote treatments against HCN include the use of sodium thiosulfate, which hastens the detoxification of CN; sodium nitrite, a methemoglobin former; and rhodanese, an enzyme

currently used in experimental trials. In some instances 100% oxygen supportive therapy in conjunction with sodium thiosulfate and sodium nitrite may be synergistically beneficial. Treatment with sodium bicarbonate can be used to reverse lactate acidosis. Ballantyne and Salem[75] provide an in-depth review of HCN exposure effects, mechanisms of action, antidotes, and sources of exposure, and Chapter 11, Cyanide Poisoning, provides additional information.

Perfluoroisobutylene

A significant exposure hazard from fires and chemical industrial accidents, PFIB causes severe pulmonary edema in the peripheral airway compartment. In mice PFIB exposure caused a significant reduction in protective sulfhydryl concentrations and myeloperoxidase activity, as well as enhancement of the influx of polymorphonuclear leukocytes into the lung.[76] Exposure can disrupt the air–blood barrier, cause hemorrhagic pulmonary edema, and increase BALF protein leak. Treatment with cholinolytic 3-quinuclidinyl benzilate 30 minutes before or 10 hours after exposure resulted in reduced indices of acute lung injury as measured by lung wet weight to body weight ratio, reduced blood viscosity and reduced mortality.

Phosgene

Because of phosgene's extensive industrial use and extreme toxicity, a great deal of experimental model development, mechanistic toxicology, and therapeutic testing has taken place over the past 25 years. Phosgene is very chemically reactive, especially with important cellular components of biomolecules, such as sulfhydryl, amine, and hydroxyl groups.[25] This chemical reactivity occurs primarily in the distal lung peripheral airway compartment, and exposure has been found to directly affect type I pneumocytes,[77,78] increase lavage polymorphonuclear phagocytes,[79] decrease both cytochrome-*c*-oxidase and adenosine triphosphatase activity,[80] and significantly reduce lung adenosine triphosphate concentrations.[81] Some limited and questionable evidence suggests that phosgene inhalation may be involved in toxic encephalopathy in humans[82]; however, this study involved long-term exposure to many chemical solvents in an industrial environment, which may have confounded the role of phosgene as a single causative agent of neurotoxicity.

Recent experimental work with phosgene in animals has shown that bronchoconstriction, enhanced pulmonary edema formation, elevated leukotriene production, increased lipid peroxidation byproducts, and decreases in both dynamic compliance and lung tissue cAMP are several of the major responses of the lung

to phosgene inhalation.[59,83,84] Phosgene has been found to be toxic through normal metabolic detoxification mechanisms unrelated to direct inhalation exposure. In hepatocytes, phosgene binds with phospholipids such as phosphatidylcholine and ethanolamine under hypoxic or normoxic conditions.[85–87] These bonds could be mechanistically important during the injury process because alveolar surfactant is largely phospholipid in content and alveolar edema causes a locally hypoxic environment. Experimental evidence has shown that phosgene exposure has a significant effect on lung surfactant levels.[88]

Based on these detrimental effects, postexposure therapeutic efforts have succeeded in reducing lung injury in exposed animals. Studies involving rodents and rabbits have shown that the effects of increased pulmonary edema, airway pressure, and pulmonary artery pressure, as well as the inhibition of the release of reactive metabolites (such as the permeability-enhancing leukotrienes, vasoactive prostaglandins, and free radicals) can all be reduced following treatment after exposure. Compounds approved by the US Food and Drug Administration such as isoproterenol, ibuprofen, aminophylline, and N-acetylcysteine can protect the lung from further damage.[33,83,89,90] In some cases, treatment can enhance survival rates.[89] No data supports the use of steroids to treat human exposure. However, medical management guidelines from the Centers for Disease Control and Prevention recommend starting intravenous corticosteroids in cases of severe exposure even if the patient is asymptomatic. Steroids administrated intravenously seem to be more beneficial when administered before exposure,[59] although this finding has yet to be tested clinically on a large scale. Not all effective treatment against phosgene-induced lung injury involves the use of drugs. In large swine exposed to phosgene, effective therapy involved the modification of ventilation parameters after exposure. Lower tidal volume, decreased ventilation rates, and decreased positive end-expiratory pressure, in addition to intravenous saline and glucose support, reduced cardiovascular effects, lung damage (reduced edema formation), and the histopathological response of the lung tissue.[40]

In addition to producing acute lung injury to the central and peripheral compartments, phosgene, chlorine, riot control agents, smokes, and ammonia can have long-term effects. Fibrosis, bronchiolitis obliterans, chronic obstructive pulmonary disease, RADS, pulmonary function abnormalities, alveolitis, and bronchiectasis are some of the sequela of exposure. The exposure could have been a one-time event, chronic exposure over years, or a multiple chemical exposure. In addition, gases such as PFIB, phosgene, and chlorine may give rise to ARDS in the days to weeks after exposure, especially

if the exposure requires intensive care intervention. Both long-term effects and the potential for developing an ARDS-like response must be taken into account in the administration of therapeutic countermeasures.

CLINICAL PRESENTATION AND DIAGNOSIS

This section considers only TICs that pose a potential threat to military personnel. Although this list is not complete, casualties from other lung-damaging agents are managed in the same way as these examples. In low doses, highly reactive TICs have a greater effect on the central airway; some TICs act on both the central and peripheral airways; and still others that are not as reactive in the central airway can defuse deeper into the respiratory tract and destroy the tissues of the alveoli-capillary membrane in the peripheral airways, leading to noncardiac pulmonary edema. Any large inhaled dose of a TIC causes both central and peripheral airway damage (Figure 10-4).

Centrally Acting Toxic Industrial Chemicals

Centrally acting chemicals affect the respiratory system from the nasopharynx to the bronchioles. Centrally acting TICs normally form strong acids or bases (alkali) with the water in the central airway tissues, which leads to the destruction of these tissues. The damaged tissue swells, causing sloughing of the epithelium lining into the airway and reactive smooth muscle contraction, causing restriction of breathing.

Levels of exposure to toxic gases are defined by the short-term exposure limit (STEL), time-weighted average (TWA), and concentrations at which toxic gasses are immediately dangerous to life or health (IDLH). STEL is the concentration of exposure that after 15 minutes may cause immediate or chronic compromise to health. TWA is the concentration for an 8-hour workday of a 40-hour workweek that most workers can be exposed to without adverse effects.[91]

Ammonia

This highly caustic and reactive gas has not been used in warfare but may be encountered in industrial accidents. Ammonia has a TWA of 25 ppm, an STEL of 35 ppm and an IDLH of 500 ppm. Most injuries from ammonia are caused by inhalation. In low doses it is primarily a centrally acting TIC (Table 10-6). Ammonia gas usually causes damage when it contacts the moist, watery tissues of the central airway, which results in the formation of a strongly alkaline solution. This reaction is exothermic—capable of causing significant thermal burns and destruction to tissues —which could lead to the victims presenting with a laryngospasm and airway collapse.

In 1941 Caplin classified accidental ammonia inhalation as mild, moderate, and severe. Casualties with mild exposure present with pain and conjunctival and upper respiratory inflammation but no signs of respi-
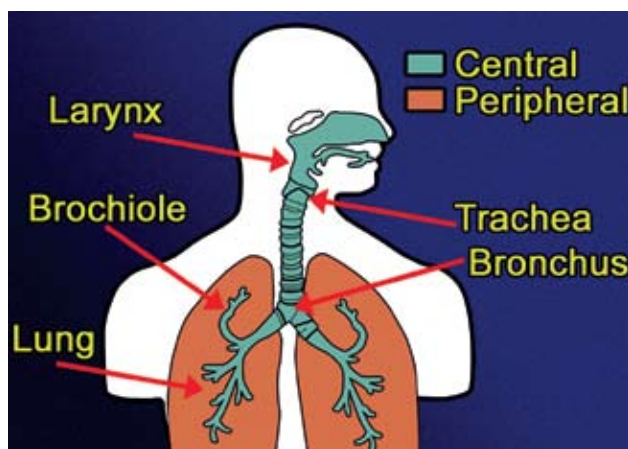
Fig. 10-4. Airway compartments: central and peripheral. Courtesy of: US Army Medical Research Institute of Chemical Defense, Aberdeen Proving Ground, Md.

TABLE 10-6

GASEOUS AMMONIA EFFECTS AT VARIOUS CONCENTRATIONS

Amount (ppm)	Effects
25–50	Detectable odor; adverse effects unlikely
50–100	Mild eye, nose, and throat irritation
140	Moderate eye irritation
400	Moderate throat irritation
700	Immediate eye injury
1,000	Directly caustic to airway
1,700	Laryngospasm
2,500	Fatal (after half-hour exposure)
2,500–6,500	Sloughing and necrosis of airway mucosa, chest pain, pulmonary edema and bronchospasm
5,000	Rapidly fatal

Data source: Issley S. Toxicity, ammonia. eMedicine from WebMD. Available at: http://www.emedicine.com/EMERG/topic846.htm. Accessed August 6, 2007.

ratory distress. Casualties with moderate exposure present with the same signs but more exaggerated symptoms. Casualties with a severe exposure present with frank respiratory distress, productive cough, pulmonary edema, and dysphagia. After a brief exposure damage is usually limited to the upper airway mucosa. However, a brief exposure at a very high concentration can be overwhelming to the victim and the entire respiratory system.

Ammonia inhalation injuries also lead to pain of the oroharyngeal and retrosternal areas. Symptoms of dyspnea, hemoptysis, hoarseness, and loss of consciousness could be noted. Tissues of the airway become swollen, and, longer term, scar tissue may form along the airway. Frequently, damaged tissue in the airway will die, slough off, and lead to obstruction. Individuals with reactive airway disease are particularly sensitive to ammonia inhalation.

Ammonia can also be absorbed by dust particles that travel to the small airways. Respiratory symptoms can develop after the ingestion of ammonia products if aspiration pneumonia or pneumonitis complicates ingestion. Most casualties who survive the first 24 hours will recover. Patients show improvement within 48 to 72 hours, and patients with mild exposure could recover fully in this time. For patients with more severe respiratory symptoms, recovery can be expected within several weeks to months.[91]

Sulfur Mustards

Produced solely for warfare, sulfur mustards are vesicants and alkylating agents that act on the central airway if inhaled. Sulfur mustards cause a dose-dependent inflammatory reaction in the upper and lower airways that develops several hours after exposure and progresses. Burning of the nasal pathway results in pain, epistaxis, larynigitis, loss of taste and smell, coughing, wheezing, and possible dyspnea. Necrosis of the respiratory epithelium causes tissue to slough off in large sheets, known as pseudomembranes, causing local airway obstruction.[92] Prolonged or repeated acute exposure to sulfur mustards could lead to chronic respiratory disease. Repeated exposures result in cumulative effects because mustards are not detoxified naturally in the body.[93] Chapter 8, Vesicants, provides more information on the medical management of sulfur mustards agents.
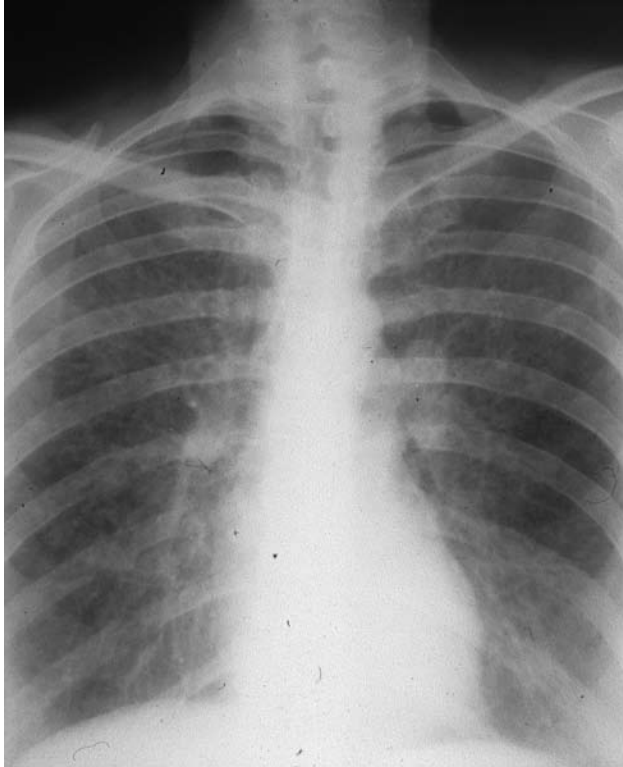
Peripherally Acting Toxic Industrial Chemicals

Air moves in the peripheral compartment of the airways only by diffusion. When peripherally acting lung-damaging TICs are inhaled, they travel to the smallest segments of the respiratory system, the terminal and respiratory bronchioles, the alveolar ducts, the alveolar sacs, and the alveoli. These agents also cause inflammation and necrosis to the thin membrane that separates the capillaries from the alveoli by reacting with the proteins and enzymes in the membranes. The function of these membranes is to separate the blood in the capillaries from the air in the alveoli, but when the membranes become damaged, this process cannot occur. When the normal elimination of plasma serum from the respiratory system is interrupted because of this damage, the plasma leaks into the alveolar septa, causing the air sacs to fill with fluid, blocking oxygen exchange. The casualty then suffers oxygen deprivation leading to hypoxia and apnea. The pulmonary tissue fills with massive amounts of fluid (up
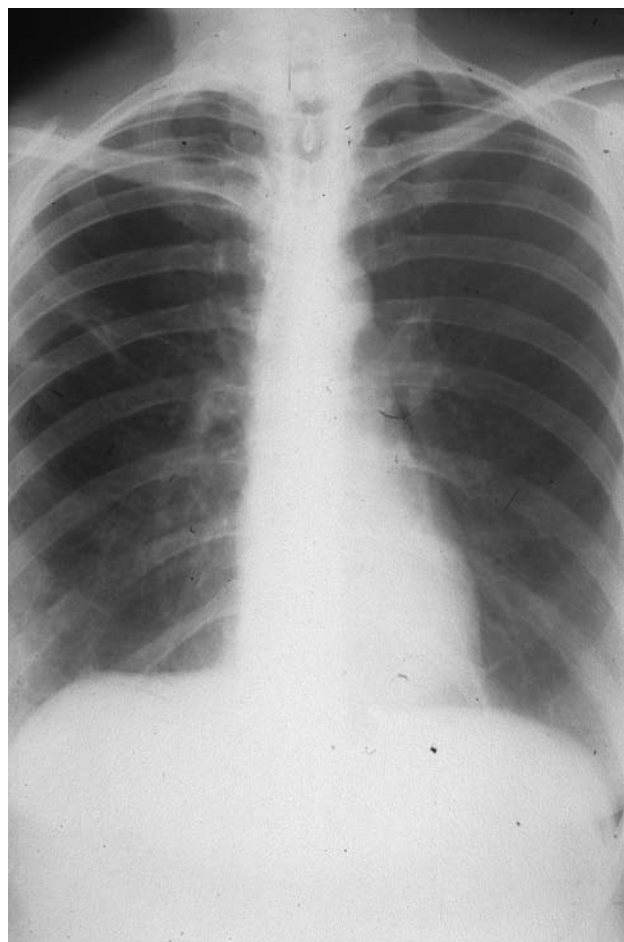
Fig. 10–5. The chest radiograph of a male chemical worker 2 hours postexposure to phosgene with mild resting dyspnea for the 2nd hour. His physical examination was normal with a P_{O_2} of 88 mm Hg breathing room air. The radiograph is normal.

Fig. 10–7. A lung section from the patient whose chest radiographs are shown in Figures 10-5 and 10-6. This section shows normal lung tissues without evidence of interstitial fibrosis or inflammation. Hematoxylin and eosin stain; original magnification × 400.
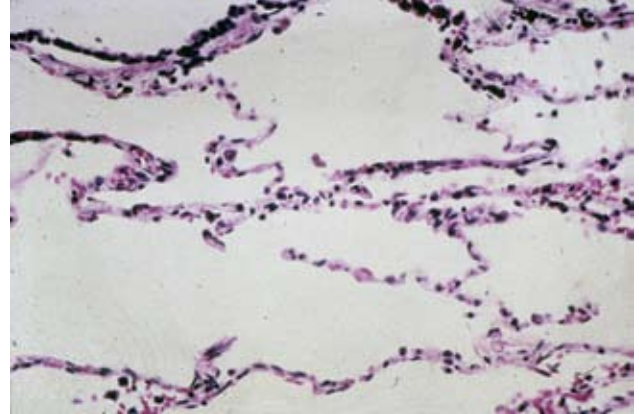
Fig. 10-6. The same patient seen in Figure 10-5 now 7 hours postexposure to phosgene with moderate resting dyspnea, a few crackles on auscultation, and a P_{O_2} of 64 mm Hg breathing room air. The radiograph shows mild interstitial edema.

to 1 L/h), which leads to noncardiogenic pulmonary edema (Figures 10-5 – 10-8). For this reason, peripherally acting TIC poisoning is sometimes referred to as "dry land drowning." The damage following acute exposure to peripherally acting lung-damaging TICs is proportionate to the product of the concentration and duration of exposure (Haber's law); however, with chronic exposure Haber's law does not apply.[1]

Perfluoroisobutylene

Produced as a common by-product in the fluoropolymer industry, PFIB is used for long-term protection against high temperatures and corrosive chemicals in automobiles, jet aircraft, and other products. Teflon's lubricity, high dielectric constant, and chemical inertness make it a desirable component for the interior of many military vehicles, such as tanks and aircraft. PFIB smoke is given off when Teflon burns at temperatures above 400°C, such as in a vehicle fire. Closed-space fires in military vehicles have prompted research on the toxicity of exposure to the by-products

Fig. 10–8. The chest radiograph of a female chemical worker 2 hours postexposure to phosgene. Dyspnea progressed rapidly over the 2nd hour; P_{O_2} was 40 mm Hg breathing room air. This radiograph shows bilateral perihilar, fluffy, and diffuse interstitial infiltrates. The patient died 6 hours postexposure.

created from incinerated organofluorines released by PFIB. The pyrolysis of PFIB produces a particulate smoke, which produces symptoms termed "polymer fume fever" when inhaled. Polymer fume fever is an influnza-like, self-limited symptom complex with a latent period of some hours followed by fever, chills, and myalgias (which could lead to the misdiagnosis of an acute viral illness). Typically, polymer fume fever episodes resolve within 24 hours; however, some cases have been reported to last longer. Only supportive care including antipyretics and hydration is recommended. If wheezing or other obstructive respiratory changes occur, inhaled bronchodilators are indicated. With bronchospasms or productive cough, inhaled steroids may be indicated. Patients with polymer fume fever should be observed for at least 24 to 48 hours for other lung consolidation changes such as chemical pneumonitis or noncardiogenic pulmonary edema. Oxygen therapy including intubation with positive end-expiratory pressure may be necessary if respiratory distress is severe. Use of antibiotic and systemic steroids should be considered, depending on the patient's condition. Survivors of vehicle fires who are short of breath should be questioned carefully about smoke exposure and should be observed over a period of time.[94]

Oxides of Nitrogen

Oxides of nitrogen, or NOx, are components of photochemical smog, which can be produced by the detonation of nitrate-based explosives or by electric or arc welding. Significant quantities of nitrogen dioxide are found in the exhaust of diesel engines. These dangerous nitrous fumes can build to high concentrations on the battlefield where artillery is fired and in enclosed spaces with inadequate ventilation, such as gun pits, ship magazines, armored vehicles, and turrets, as well as in mining and tunneling operations. Inhalation of NOx leads to the formation of nitrite, the production of methemoglobin, and cellular hypoxia. Inhalation of high concentrations could cause rapid death without the formation of pulmonary edema; however, a severe exposure may result in death with the production of yellow frothy fluid in the nasal passages, mouth, and trachea, as well as with marked pulmonary edema. Symptoms following inhalation of NOx are mostly due to nitrogen dioxide. The diagnosis is made from the history, from symptoms described by the patient, and possibly by the yellowish discoloration of the exposed membranes. NOx exposure should be suspected in soldiers who experience shortness of breath after heavy artillery firing in an enclosed space (tanks, ships).[95]

Hexachloroethane Smoke

Hexachloroethane (HC) smoke, a mixture of equal amounts of HC and zinc oxide with approximately 7% grained aluminum or aluminum powder, is used in the military for obscuration. HC smoke is probably the most acutely toxic of the military smokes and obscurants. Its toxicity is due mainly to the irritating effects of the zinc chloride. The more humid the air, the denser HC smoke will be. HC smoke is dispersed by grenades, candles, pots, artillery shells, and special air bombs.[95]

Zinc oxide cause upper respiratory tract (central compartment) damage from its irritant and corrosive action. In severe exposures, chemical pneumonia with pulmonary edema can appear. A chest radiograph of a 60-year-old sailor 8 hours after exposure to HC while in an enclosed space onboard ship shows diffuse dense peripheral pulmonary infiltrates (Figure 10-9). He had symptoms of moderately severe resting dyspnea during the 7th and 8th hours, with diffuse coarse crackles noted on auscultation.[96] Metal fume fever, which has been documented with an intense inhalation of metal oxides such as zinc oxide, has a delayed onset of 4 to 48 hours after exposure, with symptoms including dryness of the throat, coughing, substernal chest pain or tightness, and fever. Respiratory symptoms generally resolve in 1 to 4 days with supportive care. Most individuals with HC inhalation injuries progress to complete recovery; however, 10% to 20% develop fi-

Fig. 10-9. Chest radiograph taken 8 hours postexposure of a 60-year-old male sailor who inhaled zinc oxide in an enclosed space. He showed symptoms of moderately severe resting dyspnea during the 7th and 8th hours, diffuse coarse crackles on auscultation, and a P_{O_2} of 41 mm Hg breathing room air. The radiograph confirms diffuse dense peripheral pulmonary infiltrates.

brotic pulmonary changes. Appropriate precautions, such as wearing protective masks, must be taken when HC smoke is used.[95]

## Chemicals That Act on Both the Central and Peripheral Airways

Chlorine

Chlorine is a good example of a combination agent, one that acts on both airway compartments in low doses because of its intermediate water solubility. Chlorine's effectiveness as a warfare agent was greatly reduced once protective masks became widely available in World War I, but it continues to be seen in industrial accidents. The Occupational Safety and Health Administration's permissible exposure level of chlorine is 1 ppm. The National Institute for Occupational Safety and Health has determined that the IDLH concentration is 25 ppm. Chlorine turns to hydrochloric acid when it contacts the moisture of the airway; the hydrochloric acid then causes tissue burns to the epithelia of the conjunctivae and upper respiratory mucus membranes.[97] Chlorine produces signs and symptoms similar to those associated with exposure to both centrally and peripherally acting agents. A chest radiograph of a chemical worker 2 hours after exposure to chlorine shows diffuse pulmonary edema without considerable cardiomegaly (Figure 10-10). This person also experienced severe resting dyspnea and diffuse crackles on auscultation. Although the central lung damage of chlorine injury may seem to be the primary concern in some patients (ie, they are coughing and wheezing), the healthcare provider must anticipate treatment for potential development of peripheral symptoms and take seriously any patient complaints about chest tightness or breathing difficulty.[96]

Clinical Effects

Centrally Acting Agents

Almost immediately after exposure to these gasses or vapors, the casualty can develop a laryngospasm, which could cause sudden death. As the airways are irritated and damaged, the individual may experience a wide variety of symptoms including sneezing; development of rhinorrhea; tachypea; pain in the nasopharynx, indicating early inflammation; dysphagia from the pain of swallowing; oropharyngeal inflammation; hoarseness; a feeling of choking; noise with exhalation caused by laryngeal edema (the hallmark sign of cen-
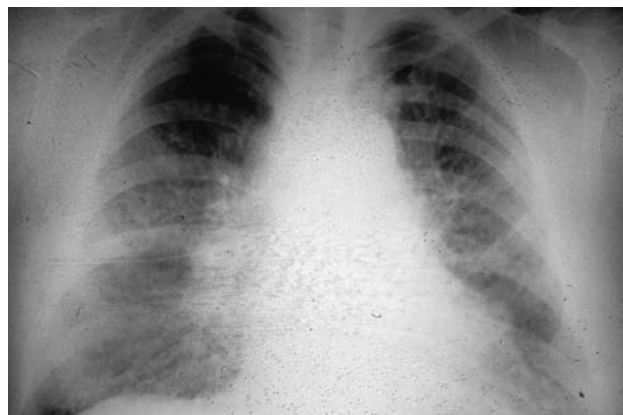
Fig. 10-10. The chest radiograph of a female chemical worker 2 hours postexposure to chlorine inhalant. On medical examination she had severe resting dyspnea during the 2nd hour, diffuse crackles/rhonchi on auscultation, and a Po_2 of 32 mm Hg breathing room air. The radiograph shows diffuse pulmonary edema without significant cardiomegaly.

trally acting agents); chest pain or retrosternal burning; coughing, which could be violent at times; wheezing during breathing from the trachea and bronchi inflammation; and edema. If the exposure is severe enough and the TIC has penetrated into the peripheral airway, the casualty may experience peripheral effects. Later, scarring of the central airway can cause permanent airway narrowing, depending on the agent involved and the dose received.

Peripherally Acting Agents

Peripherally acting agents exert a direct toxic effect on the peripheral compartment of the respiratory tract, leading to damage of the alveolar-capillary membrane and the hallmark clinical effect—dyspnea. The time to onset of clinical effects from peripherally acting agents depends on dose, duration, and concentration. Shortly after low concentration exposure to phosgene or other agents affecting the peripheral airway, the casualties are typically asymptomatic for 30 minutes to 72 hours (although they may notice irritation of the eyes, nose, and throat). However, symptoms may progress to complaints of coughing and dyspnea on exertion. The major effects do not occur until hours later. More significant exposures have a latency period of less than 24 hours. Chlorine, which can affect both compartments but primarily affects the central compartment of the respiratory tract, can also exhibit delayed effects in the peripheral compartment.

Approximately 2 to 24 hours after exposure, the ca-

sualty with peripheral damage will notice shortness of breath and tightness in the chest, which are symptoms of the development of noncardiogenic pulmonary edema. These symptoms may initially be mild, but as the damage progresses, dyspnea on exertion will become resting dyspnea. Coughing is at first nonproductive with chest tightness or discomfort described as retrosternal burning, but if the damage is severe, the casualty will start producing clear to yellow frothy sputum. This is caused by necrosis and inflammation of the lower airway and alveolar tissue and subsequent leakage of serum into the alveolar septa.

The eventual severity of dyspnea is related to dose, concentration, and duration of the exposure. A casualty with a very mild exposure will develop dyspnea 6 to 24 hours after exposure, first noticed after heavy exertion. Later, however, the casualty becomes short of breath after any activity. With proper care, complete recovery is expected. A casualty with a severe exposure will notice shortness of breath within 4 to 6 hours after exposure. Dyspnea, even at rest, results from inability of the pulmonary lymph system to eliminate the large amount of fluid produced from the necrosis of the alveolar-capillary membrane. This leads to the clinical presentation of noncardiogenic pulmonary edema, causing hypoxia and apnea. These casualties, even with intensive pulmonary care, may not survive.

Many of the casualties exposed to lung-damaging agents are between these two extreme situations. When the onset of dyspnea is more than 6 hours after exposure, there may be progression to dyspnea at rest. However, with good pulmonary care beginning early after the onset of effects, the casualty should recover completely. Failure to consider the asymptomatic period and delayed onset of peripherally acting lung-damaging agents may lead to early discharge from the emergency room, without an adequate period of observation, and possibly to a poor outcome.[1]

Diagnostic Tests

No commonly available laboratory tests exist for the specific identification or quantification of exposure to lung-damaging agents; however, an increase in the hematocrit may reflect the hemoconcentration induced by transudation of fluid into the pulmonary parenchyma from the peripherally acting agents. Arterial blood gases may show a low Pao_2 or $Paco_2$, which is an early, nonspecific warning of increased interstitial fluid in the lung. Peak expiratory flow rate may decrease early after a massive exposure to peripherally acting agents. This nonspecific test helps assess the degree of airway damage and the effect of bronchodilator therapy. Decreased lung compliance and carbon monoxide diffusing capacity are particularly sensitive indicators of interstitial fluid volume in the lung, but because of their complexity, these tests are usually performed only in hospitals.

Chest Radiograph

Initial findings on a chest radiograph may be normal; as the disease process progresses, the radiograph may demonstrate bilateral diffuse interstitial infiltrates. The early finding on a chest radiograph is hyperinflation, which suggests toxic injury of the smaller airway that results in air being diffusely trapped in the alveoli. The appearance of "batwing" infiltrates is caused by pulmonary edema secondary to the alveolar capillary membrane damage. Pulmonary edema develops later and without cardiovascular changes of redistribution or cardiomegaly. Radiological changes from centrally acting lung-damaging agents may occur for hours to days, so the use of a chest radiograph may be of limited value.

Arterial Blood Gases

Measuring carboxyhemoglobin and methemoglobin levels can help determine whether the casualties have been exposed to methylene chloride or confirm suspected carbon monoxide exposure; methemoglobinemia may suggest other causes. Serial arterial blood gases in cases of significant respiratory distress demonstrate the degree of hypoxemia. Hypoxia is often the result of exposure to both centrally and peripherally acting lung-damaging agents. The measurement of the partial pressure of oxygen (Po_2) can give insight into the treatment of hypoxia, but it is a nonspecific tool in the diagnosis of exposure to a lung-damaging agent.[1]

Pulmonary Function Tests

A variety of airway and pulmonary parenchymal function measures can be performed in rear-medical treatment facilities. Initial and follow-up measurements of the flow-volume loop, lung volumes, and lung diffusing capacity for carbon monoxide are particularly useful in assessing and managing long-term effects of a lung-damaging TIC exposure. Although such laboratory studies are of minimal value in an acute-care setting, flow-volume loop measures may document a previously unrecognized degree of airway obstruction. A degree of reversibility may also

be demonstrated if bronchodilators are tested at the same time. Substantial airway obstruction may be present with little clinical evidence. In all cases of unexplained dyspnea, regardless of clinical findings, careful pulmonary function measurements should be undertaken. Ideally, these studies should be performed in an established pulmonary function laboratory and would include lung diffusing capacity for carbon monoxide and arterial blood gas measurements. These studies should also be performed during exertion if the patient has dyspnea on exertion that cannot otherwise be explained by pulmonary function studies performed at rest.[1]

Bronchoalveolar Lavage

Bronchoalveolar lavage is a diagnostic procedure that involves washing a sample of cells and secretions from the alveolar and bronchial airspaces. An inflammatory response can be detected by polymorphonuclear leukocytes and an increase in protein content in the lung washings. Cell death or membrane damage can be indicated by the release of cytoplasmic enzymes and lactate dehydrogenase into the acellular portion of the lavage fluid. Animals chronically exposed to insoluble particles show a large increase in some lysosomal enzymes found in the bronchoalveolar lavage fluid. Also, angiotensin-converting enzymes have been found to be elevated with endothelial cell damage in the pulmonary capillaries. Although bronchoalveolar lavage has been used to validate the presence of acute lung injury from TICs, the method is limited by the large range of normal values for each parameter.[53]

Other Tests

- Pulmonary capillary wedge pressure should be monitored in cases of severe pulmonary edema or ARDS.
- Ventilation/perfusion scans can show abnormal air trapping in the setting of lower airway obstruction and may be useful to help gauge severity or progress of respiratory disease; however, these findings are unlikely to change acute medical management.
- Carbon dioxide levels should be monitored in patients with prior lung disease such as asthma and chronic obstructive pulmonary disease; these patients may be affected more severely and are at greater risk of retaining carbon dioxide.

MEDICAL MANAGEMENT

Lung-damaging TIC casualties may have minimal signs and symptoms during the acute phase, and the prognosis should be guarded. Ongoing reassessment is an essential component of the early medical management of these casualties, for they could rapidly develop severe noncardigenic pulmonary edema. However, many of the casualties who survive for more than 48 hours recover without sequelae. A complete medical history is one of the most important aspects in the medical management of these casualties. In contrast to most occupational inhalational exposures, lung-damaging chemical warfare agents need specific immediate treatment in addition to the usual supportive care (the suspicion of exposure to lung-damaging chemical warfare agents is of course higher in times of war or terrorist activity).

Patient History

Collecting historical data from the casualty is a critical aspect of assessing and treating individuals exposed to lung-damaging agents. No specific statement can determine the correct diagnosis and ultimate treatment, but careful questioning of an exposed individual will often greatly simplify the diagnosis and medical therapy. Different approaches to collecting a history may be needed depending on the circumstances of the events involved (see Exhibit 10-1 for a list of example questions). If a casualty is unable to provide a history of the incident, an observation of the scene can be helpful in determining treatment, the amount of time needed for observation, and the likely prognosis. Other personnel on the scene of the incident, who may have conducted reconnaissance or any atmospheric monitoring, may be able to assist in the clinical decision making.

Physical Examination

Physical examination may be particularly difficult in the event of combined lung-damaging TICs and conventional injuries; therefore, it is essential that medical personnel note the patient's physical condition (specific conditions to look for are listed in Exhibit 10-2). Symptoms of lung-damaging TIC inhalation injuries can be delayed in onset, but some conditions that may precede the onset of delayed symptoms include facial burns, inflamed nares, wheezing, altered mental status, and productive cough. Coughing will more than likely be the first symptom noted (although an occasional

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EXHIBIT 10–1

HISTORY ASSESSMENT FOR CASUALTIES EXPOSED TO LUNG-DAMAGING AGENTS

- **Environment**: Were the explosions observed? Was there obvious smoke? If so, what color was it? Was the smoke heavier than air or close to the ground? What was the weather condition (temperature, rain, wind, daylight, fog)? Were there pools of liquid or a thickened substance in evidence?
- **Protective posture:** What was the level of mission-oriented protective posture (MOPP)? Was there face mask or suit damage? Did the face mask fit adequately? When was the filter last changed? How well trained was the indivual in using the appropriate protective posture? Were other factors present (eg, consumption of alcoholic beverages, exposure to other chemicals, psychiatric status)?
- **Prior exposure:** Was there prior exposure to other chemical agents? Is the individual a cigarette smoker? (For how many years? How recently did he or she last smoke? How many cigarettes smoked a day?)
- **Pulmonary history:** Is there a prior history of chest trauma, hay fever, asthma, pneumonia, tuberculosis, exposure to tuberculosis, recurrent bronchitis, chronic cough or sputum production, or shortness of breath on exertion?
- **Cardiac and endocrine history:** Is there a history of cardiac or endocrine disorder?
- **Acute exposure history:** What were the initial signs and symptoms?
  ° **Eyes:** Is there burning, itching, tearing, or pain? How long after exposure did symptoms occur: minutes, hours, days?
  ° **Nose and sinuses:** Was a gas odor detected? Is there rhinorrhea, epistaxis, or pain? How long after exposure did symptoms occur: minutes, hours, days?
  ° **Mouth and throat:** Is there pain, choking, or cough? How long after exposure did symptoms occur: minutes, hours, days?
  ° **Pharynx and larynx:** Are there swallowing difficulties, cough, stridor, hoarseness, or aphonia? How long after exposure did symptoms occur: minutes, hours, days?
  ° **Trachea and mainstem bronchi:** Is there coughing, wheezing, substernal burning, pain, or dyspnea? How long after exposure did symptoms occur: minutes, hours, days?
  ° **Peripheral airways and parenchyma:** Is there dyspnea or chest tightness? How long after exposure did symptoms occur: minutes, hours, days?
  ° **Cardiac:** Are there palpitations, angina, or syncope? How long after exposure did symptoms occur: minutes, hours, days?
  ° **Central nervous system:** Is there diffuse or focal neurological dysfunction?

Data source: Bickley LS, Szilagyi PG. *Bates' Guide to Physical Examination and History Taking*. 9th ed. Philadelpha: Lippincott-Raven; 2005.

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cough may be a symptom of asthma).

Acute Medical Management

Exposure to lung-damaging agents can be limited by removing casualties from the environment in which the toxicant is present. Careful decontamination serves to limit reexposure to the toxicant from body surfaces or clothing, as well as reducing the risk of secondary exposure of healthcare personnel. Listed below are important steps in the acute management of lung-damaging agents. See Exhibit 10-3 for triage procedures.

Terminate Exposure and Decontaminate

The first vital measure is to physically remove the casualty from the contaminated environment or properly fit the person with a protective mask. Decontami-

nation starts with the staff and decontamination team in the appropriate protective gear. Decontamination of any liquid agent on skin and removal of clothing (where agent vapors could be trapped) will fully terminate the exposure from these sources. Removal of the casualty's clothing, if it has been contaminated with liquid agent, prevents cross contamination of any unprotected staff or casualty. If eye involvement is reported, remove contact lenses, if present, and irrigate with copious amounts of water or saline. If the skin exposure is significant, wash with copious amounts of water and mild soap.[97]

Implement ABCs

Establishing an airway is especially crucial in a patient exhibiting hoarseness or stridor; such individuals may face impending laryngeal spasm. Establishing a

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EXHIBIT 10-2

PHYSICAL ASSESSMENT FOR CASUALTIES OF LUNG-DAMAGING CHEMICAL AGENTS

- **Reliability:** Is the casualty alert and oriented?
- **Appearance**: Is the casualty anxious or tachypneic?
- **Vital Signs:** What are the casuality's weight, blood pressure, pulse, temperature and pulse oximetry?
- **Trauma:** Is there a head injury? Are there burns in the region of the eyes, nose, or mouth?
- **Skin**: Are there signs of burns, erythema, cyanosis, sweating, or dryness? Are there facial or oral burns and ulceration?
- **Eyes**: Is there conjunctivitis, corneal burns or abrasion, lacrimation, miosis, or mydriasis?
- **Nose**: Is there erythema, rhinorrhea, or epistaxis?
- **Oropharynx**: Is there evidence of perioral burns or erythema?
- **Neck**: Is there hoarseness, stridor, or subcutaneous emphysema?
- **Chest**: Is there superficial chest wall trauma, tenderness, crepitation, dullness, or hyperresonance? Palpitatons? Angina?
- **Respiration**: Is tachypnea present? What is the oxygen saturation? Is the a productive cough (with phosgene, cough is initially nonproductive, later frothy white to yellow sputum) Hemoptysis? Are inspiratory crackles, wheezes, rhonchi present?
- **Central nervous system:** Is there loss of consciousness? Headache (thought to be secondary to hypoxemia and the inflammatory response initiated in the pulmonary parenchyma)?

Data source: Bickley LS, Szilagyi PG. *Bates' Guide to Physical Examination and History Taking*. 9th ed. Philadelpha: Lippincott-Raven; 2005.

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clear airway also aids in interpretation of auscultatory findings. Steps to minimize the work of breathing must be taken. Because of the always present danger of hypotension induced by pulmonary edema or positive airway pressure, accurate determination of the casualty's circulatory status is vital not only initially, but also at regularly repeated intervals and whenever indicated by the clinical situation.

Implement Rest

Even minimal physical exertion may shorten the clinical latent period and increase the severity of respiratory symptoms and signs in a lung-damaging agent casualty. Physical activity in a symptomatic patient may precipitate acute clinical deterioration and even death. Strict limitation of activity (eg, forced bed rest) and litter evacuation are mandatory for patients suspected of having inhaled any of the edematogenic agents. This is true whether or not the patient has respiratory symptoms and whether or not objective evidence of noncardiogenic pulmonary edema is present.

Manage Airway Secretions; Prevent and Treat Bronchospasm

Unless superinfection is present, secretions present in the airways of lung-damaging agent casualties are usually copious and watery. Secretions may serve as an index to the degree of noncardiogenic pulmonary edema and do not require specific therapy apart from suctioning and drainage. Antibiotics should be reserved for patients with an infectious process documented by sputum Gram staining and culture. Bronchospasm may occur in individuals with reactive airways and should be treated with theophylline or beta-adrenergic bronchodilators. Steroid therapy is also indicated for bronchospasm but must be parenterally administered; inhaled therapy may result in inadequate distribution to damaged airways. Methylprednisolone, 700 to 1,000 mg, or its equivalent may be given intravenously in divided doses during the first day and then tapered during the duration of the clinical illness. The increased susceptibility to bacterial infection during steroid therapy mandates careful surveillance of the patient. There is some support in the literature for steroid use in those exposed to HC smoke (zinc/zinc oxide) and oxides of nitrogen, because steroids can theoretically reduce autoimmune reactions that foster scar development and subsequent bronchiolitis obliterans. In the case of phosgene exposure, the literature suggests that corticosteroid administration in the first 15 minutes postexposure reduces the degree of noncardiogenic pulmonary edema.[98] The literature does not give strong support for the use of steroids in the treatment of other toxic inhalants because steroids reduce lung bacterial clear-

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EXHIBIT 10-3

TRIAGE FOR CASUALTIES OF LUNG-DAMAGING TOXIC INDUSTRIAL CHEMICALS

Patients Seen Within 12 Hours of Exposure

- **Immediate**: Patients with pulmonary edema only, and if intensive pulmonary care is immediately available. In general, a shorter latent period portends a more serious illness.

- **Delayed:** Patients who are dyspneic without objective signs should be observed closely and retriaged hourly if not sooner.

- **Minimal**: Asymptomatic patients with known exposure, these patients must be observed and retriaged every 2 hours. If a patient remains asymptomatic 24 hours after exposure, the patient could be discharged. If exposure is doubtful and the patient remains asymptomatic 12 hours following putative exposure, consider discharge.

- **Expectant:** Patients who present with pulmonary edema, cyanosis, and hypotension are classified as expectant. A casualty who presents with these signs within 6 hours of exposure generally will not survive; a casualty with the onset of these signs 6 hours or longer after exposure may possibly survive with immediate, intensive medical care. If ventilatory support is not available, but adequate evacuation assets are, these patients should have priority for urgent evacuation to a facility where adequate ventilatory support is available.[1]

Patients Seen More Than 12 Hours After Exposure

- **Immediate:** Patients who present with pulmonary edema, if they can receive intensive care treatment within several hours.

- **Delayed:** Patients who are dyspneic should be observed closely and retriaged at least every 2 hours. Patients who are recovering from the exposure could be discharged 24 hours after exposure.

- **Minimal:** Patients who are asymptomatic or have resolving dyspnea are classified as minimal. Patients who are asymptomatic 24 hours after exposure may be discharged.

- **Expectant:** Patients who present with persistent hypotension despite intensive medical care interventions. If cyanosis and hypotension are present with pulmonary edema, triage the patient as expectant.

Examples: Patients with only eye or upper airway irritation who are otherwise asymptomatic and with normal physical examination 12 hours later may be returned to duty. If the patient's original complaint was dyspnea only and on physical examination the chest radiograph and arterial blood gases are all normal at 24 hours, he or she may be returned to duty. Patients who presented with symptoms of an abnormal physical examination, chest radiograph, or arterial blood gas require close supervision; however, if physical examination, chest radiograph, and arterial blood gases are all normal at 48 hours, they can be returned to duty.

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(1) US Army Medical Research Institute of Chemical Defense. *Medical Management of Chemical Casualties Handbook.* 4th ed. Aberdeen Proving Ground, Md: USAMRICD; 2007.

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ance and increase the potential for bacterial pneumonia as a late complication of inhalation injuries, which outweighs any potential antiinflammatory effects. Thus, steroids are not recommended in individuals without evidence of overt or latent reactive airway disease.[99]

Prevent and Treat Pulmonary Edema

Positive airway pressure provides some control over the clinical complications of pulmonary edema. Early use of a positive pressure mask may be beneficial. Positive airway pressure may exacerbate hypotension by decreasing thoracic venous return, necessitating intravenous fluid administration and perhaps judicious use of a pneumatic antishock garment.

Prevent and Treat Hypoxia

Oxygen therapy is definitely indicated and may require supplemental positive airway pressure administered via one of several available devices for generating intermittent or continuous positive pressure. Intubation, with or without ventilatory assistance, may be required, and positive pressure may need to be applied during at least the end-expiratory phase of the ventilator cycle. Humidified oxygen supplementation may be needed.

Prevent and Treat Hypotension

Sequestration of plasma-derived fluid in the lungs

may cause hypotension that may be exacerbated by positive airway pressure. Due to fluid shifts, urgent intravenous administration of either crystalloid or colloid solution (which in this situation appear equally effective) and the use of a pulmonary artery catheter monitor (to avoid excessive fluid administration) may be required to maintain appropriate fluid balance while treating hypotension. The use of vasopressors is a temporary measure until fluids can be replaced.

Clinical Care

Acute lung injury is one of the causes of noncardiogenic pulmonary edema, which causes an increase in lung vascular permeability, leading to accumulation of protein-rich edema in the interstitial and air spaces. Cardiogenic or high-pressure pulmonary edema is caused by elevated pulmonary venous pressure from left ventricular dysfunction, valvular disease, or intravascular volume overload. In addition to ARDS, noncardiogenic pulmonary edema is referred to as "clinical acute lung injury." The care of these patients requires careful attention to the underlying causes such as a treatable pulmonary infection. The modes of mechanical ventilation and hemodynamic manage-

ment in ARDS patients have been controversial for years, although the National Institutes of Health and other institutions have established a protocol for ARDS patients on mechanical ventilation. Discussion of this protocol and any other strategies is beyond the scope of this chapter; however, one certainty is that ARDS management demands quick recognition and intensive care protocols.[100,101]

Patient Transport

Lung-damaging TIC casualties may need to be evacuated to a higher level of care if the receiving facility does not have an intensive care setting. When a casualty is transferred to a higher level of care, supplemental oxygen and appropriate evaluation monitors must be provided.

Long-Term Effects

The replacement of damaged airway epithelium with granular tissue is one of the major etiologies of chronic lung disease following centrally acting chemical agents such as ammonia.[91] See Chapter 9, Long-Term Health Effects of Chemical Threat Agents, for more detail.

SUMMARY

The respiratory system, both the central and peripheral compartments, can efficiently absorb inhaled lung-damaging agents, leading to airway and pulmonary injury. Few specific antidotes exist for treating inhaled toxicants. Common pathophysiologic pathways link

the syndrome of acute inhalation injury to preferential methods of clinical treatment. Understanding the mechanisms of inhalation injury can simplify the decision-making process for treating a casualty with a potential lung-damaging TIC inhalation exposure.

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